CLINICAL STUDY PROTOCOL

Study Title:	Evaluation of the Efficacy and Safety of GS-5745 as Add-On Therapy to a Tumor Necrosis Factor Inhibitor and Methotrexate Regimen in Subjects with Moderate to Severe Rheumatoid Arthritis	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404	
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	110523 2016-000897-39 NCT0286574	
Indication:	Rheumatoid Arthritis	
Protocol ID:	GS-US-373-1499	
Gilead Study Director or Clinical Program Manager:	Name: Telephone: Fax: Mobile:	PPD PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile:	David Gossage, MD PPD PPD PPD
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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study Title:	Evaluation of the Efficacy and Safety of GS-5745 as Add-On Therapy to a Tumor Necrosis Factor Inhibitor and Methotrexate Regimen in Subjects with Moderate to Severe Rheumatoid Arthritis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	110523 2016-000897-39 NCT0286574
Study Centers Planned:	Approximately 40 centers globally
Objectives:	The primary objective of this study is as follows: To assess the efficacy of GS-5745 versus placebo as an add-on therapy to a TNF inhibitor and methotrexate in subjects with moderately to severely active rheumatoid arthritis (RA) The secondary objectives of this study are as follows: • To assess the safety and tolerability of GS-5745 versus placebo as an add-on therapy with a TNF inhibitor and methotrexate (MTX) in subjects with moderately to severely active RA • To assess the pharmacokinetics (PK) of GS-5745 as an add-on therapy with a TNF inhibitor and methotrexate (MTX) in subjects with moderately to severely active RA The exploratory objectives of the study are as follows: PPD [redacted]
Study Design:	This is a Phase 2, double-blind, placebo-controlled, randomized multi-center study evaluating the efficacy and safety of GS-5745 as add-on therapy in subjects with moderately to severely active RA who have had an inadequate response to anti-TNF biologic therapy (TNF-IR).

	Subjects will be stratified by Disease Activity Score for 28 joints, either DAS28(CRP) > 5.1 or DAS28(CRP) > 3.2 and ≤ 5.1. In addition, subjects will be stratified by the prior number of RA biologics used (< 3 or >= 3). Subjects will receive SC injections of study drug (GS-5745 or placebo) once a week for 12 weeks in the blinded period. Eligible subjects who complete the blinded period of the study may participate in the optional open-label extension (OLE), where they will receive weekly subcutaneous (SC) injections of 300 mg of GS-5745 for 52 weeks, in addition to continuing their current TNF inhibitor and MTX.
Number of Subjects Planned:	Approximately 75 subjects
Target Population:	Subjects with moderately to severely active RA currently treated with a stable dose of TNF inhibitor for at least 12 weeks and methotrexate (MTX) currently treated for at least 12 weeks and on a stable dose for at least 6 weeks at Screening.
Duration of Treatment:	Subjects will receive SC injections of study drug (GS-5745 or placebo) once a week for 12 weeks in the blinded period and weekly injections of study drug (GS-5745) through Week 64 in the OLÉ.
Diagnosis and Main Eligibility Criteria:	For a complete list of inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3. **Key inclusion criteria include:** • Male or female subjects between 18 and 80 years of age inclusive, at time of signing initial informed consent • Diagnosis of RA (according to the 2010 ACR/EULAR classification criteria (See Appendix 8) confirmed at Screening • Must have taken oral or parenteral MTX dosed from 7.5 to 25 mg/week continuously for at least 12 weeks and tolerated this medication, with at least 6 weeks of stable dose (defined as no change in prescription) prior to first dose of study drug • Subjects on MTX may also be on concurrent chloroquine or hydroxychloroquine at a stable dose (defined as no change in prescription) for at least 4 weeks prior to Baseline; if so, they should plan to continue this medication for the duration of the study

- Must have an inadequate response to ≥ 12 weeks of ongoing treatment with an approved dose of SC formulation of TNF inhibitor (adalimumab, certolizumab pegol, etanercept, or golimumab), or marketed SC biosimilar TNF inhibitor with at least 6 weeks of stable dose (defined as no change in prescription), defined as:
    - Must have a DAS28(CRP) > 3.2 at Screening

      AND
    - Must have ≥ 3 swollen joints and ≥ 3 tender joints (using the DAS28 joint counts) at Screening and at Baseline (do not need to be the same joints)
- Non-steroidal anti-inflammatory drugs (NSAIDs) and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent) at a stable dose (defined as no change in prescription) for ≥ 4 weeks prior to Baseline are allowed and should be continued throughout the blinded period of the study; PRN NSAID for indications other than RA are also allowed
- TB Screening: Subjects must meet either a. or b.:

  a. A negative history of TB infection and a negative QuantiFERON® TB-Gold In-Tube test and chest x-ray results (see below). (QuantiFERON® tests with inconclusive results may be repeated one time. If the repeat result is also inconclusive, the subject will be excluded from the study.

  OR,

  b. Subjects with a history of **latent** TB treated with a full course of prophylaxis as per local guidelines are allowed per investigator judgment. It is the responsibility of the investigator to verify the adequacy of previous treatment and to provide appropriate documentation. *In these cases, no QuantiFERON® test need be obtained.* In addition, these cases must be approved by the medical monitor prior to enrollment. . (Any new diagnosis of latent TB or prior untreated /partially treated latent TB in NOT allowed (ie, subjects who require prophylactic therapy for TB during the study). Any prior history of **active** TB [regardless of treatment] is exclusionary).
- A negative chest x-ray (views per local guidelines) for active TB or other lung disease at Screening; or a chest x-ray within 90 days of Screening if films or report are available for investigator review

- Subjects of child-bearing potential (as defined in protocol) must agree to use protocol specified contraceptive measures throughout the study and for 30 days after their last dose of study drug. Female subjects must agree not to become pregnant for 30 days after the last dose of study drug. Female subjects taking MTX or other drugs should also follow contraception guidelines in the relevant product local label (see Appendix 5)

Key exclusion criteria include

- Current treatment with any disease modifying anti-rheumatic drug (DMARD) other than MTX, chloroquine or hydroxychloroquine , or current treatment with other immune modulating/suppressive non-biologic and biologic medications as described in Section 5.4.4
- Intra-articular corticosteroid injection of any joint within 4 weeks of Baseline
- Any infection requiring oral antimicrobial therapy within 2 weeks prior to Baseline
- Current inflammatory joint disease other than RA, (such as gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthritis, or Lyme disease), **OR** other current autoimmune disease (such as: systemic lupus erythematosus (SLE), inflammatory bowel disease, polymyalgia rheumatica, scleroderma, inflammatory myopathy, mixed connective tissue disease, or other overlap syndrome) that would interfere with the evaluation of RA or require protocol prohibited medication; subjects with Sjogren's syndrome or controlled thyroiditis are not excluded
- Active systemic involvement secondary to RA, such as vasculitis or Felty's syndrome
- History of any of the following within 12 months of Baseline:
  a) infection requiring parenteral antibiotics or hospitalization,
  b) any life-threatening infection,
  c) sepsis
- Tests performed at the central laboratory during Screening that meet any of the criteria below:
  a) Hemoglobin <8.0 g/dL (International System of Units [SI]: <80 g/L);
  b) White blood cells $<3.0 \times 10^3$ cells/mm^3 (SI: $<3.0 \times 10^9$ cells/L);

c) Neutrophils <1.5 x 10^3 cells/mm^3 (SI: <1.5 x 10^9 cells/L);

d) Lymphocytes <0.5 x 10^3 cells/mm^3 (SI: <0.5 x 10^9 cells/L);

e) Platelets <100 x 10^3 cells/mm^3 (SI: <100 x 10^9 cells/L);

f) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2x ULN;

g) Total bilirubin level ≥2x ULN, unless the subject has been diagnosed with Gilbert's disease and this is clearly documented;

h) Estimated glomerular filtration rate <40 mL/min/1.73m^2 based on the Modification of Diet in Renal Disease (MDRD) formula. (See Appendix 10)

i) Positive HIV serology during Screening

j) Evidence of active Hepatitis B Virus (HBV) infection

k) Evidence of active Hepatitis C Virus (HCV) infection

- Any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study, per judgment of investigator
- Any chronic, uncontrolled medical condition which would put the subject at increased risk during the study participation such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per judgment of the investigator
- Malignancy or lymphoproliferative disorder within 10 years of Screening, except:

  a) Carcinoma in situ of the cervix that has been successfully treated

  b) Adequately treated basal or squamous cell cancer that has been successfully treated

Study Procedures/ Frequency:

All subjects will have the following visits at the study site during the blinded period of the study: Screening, Day 1 (first dose of study drug) and Weeks 1, 4, 8 and 12. Subjects will receive the first two injections of study drug (Day 1 and Week 1) at the study site. After completion of the 12 week blinded period of the study, subjects will have the option to participate in the OLE in the same protocol. Subjects who do not participate in the OLE will complete Week 12 assessments and will not receive open label study drug. These subjects

will have a follow up visit 30 days after their last dose of study drug.

Subjects who are eligible will receive their first dose of OLE study drug at Week 12, after completing all the required assessments of the Week 12 visit. Additional OLE study visits will occur at Weeks 13, 19, 24, 30, 36, 42, 48, 54, 60, and 64, with a follow-up visit 30 days after the subject's last dose of study drug.

Screening Assessments

- Confirmation of RA diagnosis
- Medical/Surgical history
- Vital signs to include blood pressure, pulse, temperature and respiration
- Complete physical exam (CPE) height and weight
- 12 lead ECG
- Central laboratory tests including Rheumatoid Factor, anti-CCP, complete blood count, hematology, chemistry panel, urinalysis, urine drug screen, serum ß-HCG (women of childbearing potential), QuantiFERON® TB-Gold In-Tube test , HIV, Hepatitis B and C testing (with reflex testing if positive for antibodies), CRP, Estimated Glomerular Filtration Rate (based on MDRD study equation), TSH and HbA1c. Flow cytometry for absolute CD19+ B-cell counts (subjects who have taken rituximab or any B cell depleting agent)
- A negative chest X-ray (views per local guidelines) for active lung disease at Screening; or a chest X-ray within 90 days of Screening if films and/or report are available for investigator review.
- 66 swollen and 68 tender joint counts
- Patient's and Physician's Global Assessment of Health
- Patient's Assessment of Pain

On-Treatment Assessments

- Concomitant medications
- Vital signs to include blood pressure, pulse, temperature, respiration, and weight
- CPE (Blinded period Week 12 and Week 64 only); targeted Physical exam (TPE) at all other visits
- 12-lead ECG (Week 12 blinded period and Week 64 only)
- Clinical laboratory testing, to include: Hematology, urinalysis, chemistry panel and CRP (blinded period Study Day 1, Weeks 1,

4, 12, and the 30-day follow-up), Estimated Glomerular Filtration Rate (based on MDRD study equation will be calculated week 12 , 30 day follow-up and ESDD. In the OLE hematology, urinalysis, chemistry, CRP labs will be checked every 6 weeks and at the 30-day follow-up visit , Estimated Glomerular Filtration Rate (based on MDRD study equation) will be calculated at weeks 24, 26, 28 and 60 and the ESDD .

- Subjects with positive HBV Core Ab and/or HCV Ab during screening are to have the respective DNA or RNA PCR test every 3 months during the study. A positive test for hepatitis virus should lead to study discontinuation as per Section 3.5.2
- Serum β-HCG pregnancy test (at Week 12 and at the 30-day follow-up and ESDD), and urine pregnancy tests (at Day 1 and every 4 weeks) in women of child-bearing potential. For urine pregnancy tests performed at home, the site will contact the subject to confirm the urine pregnancy test was performed and will document the result as per protocol. Subjects may also present to the site for the urine pregnancy testing if they prefer.
- In the blinded period, questionnaires and disease activity measures will be administered at Day 1, Weeks 1, 4, 8, 12, ESDD and at the 30-day follow-up visit. In the OLE, these assessments will be performed every 12 weeks, at Week 64, ESDD and at the 30-day follow-up visit.

Study Drug Administration:

Blinded Period

SC study drug administration will occur at the study site on Day 1, Weeks 1, 4, and 8. Subjects will remain at the study site for at least 30 minutes after the first 2 injections of study drug for observation. This time may be extended per judgment of the investigator. After receiving SC instruction at the study site during the first 2 study drug injections, subjects (or their caretakers) who are judged capable, will be allowed to self-administer SC injections at home during the weeks where on-site visits are not scheduled.

Open Label Extension (OLE)

In the OLE, study drug administration will occur weekly from Week 12 to Week 64. SC study drug administration will occur at the study site for the first 2 doses in the OLE at Weeks 12 and 13. Subjects will remain at the study site for at least 30 minutes after the first 2 injections of study drug for observation. This time may be extended per judgment of the investigator. (Subjects are to be scheduled for a 30-day follow-up visit after their last dose of study

	drug. Routine SC administration of the subject's own TNF inhibitor identified during Screening should continue throughout the study, as per the local label. <u>PK and Biomarker Sampling:</u> *PK Blood Draws*: PK blood draws will be done prior to dosing at Weeks 1, 4, and 8, anytime at Week 12 and at ESDD (if applicable), prior to dosing at Week 24 and anytime at Week 64 of the OLE. Optional PK Sub-study: PPD *Anti-GS-5745 Antibodies (ADA)*: Blood draws for ADAs will be done prior to dosing on Day 1, Weeks 4 and 8; and anytime at Week 12, and the 30-day follow-up visit of the blinded period. Blood draws for ADAs will be done prior to dosing at Week 24, and anytime at Week 64, the 30-day follow-up visit of the OLE. *Biomarker Blood Draws*: Blood for biomarkers will be collected during the blinded period at Day 1 and, Weeks 4 and 12. For During the OLE, samples will be collected every 3 months, starting at Week 24. *TB testing:* A repeat QuantiFERON® TB-Gold In-Tube test will be performed annually (Week 54) for subjects continuing in the study. A repeat chest x-ray may also be performed annually, depending upon local TB screening guidelines. <u>Genomic Testing</u> *Optional Genomic Testing*: PPD
Test Product, Dose, and Mode of Administration:	**Group 1:** GS-5745 300 mg (2 x 1 mL GS-5745 [150 mg/ml] SC injections) administered weekly **Group 2:** GS-5745 150 mg (1 x 1 mL GS-5745 [150 mg/ml] + Placebo-to-match 1 x 1 mL SC injections) administered weekly
Reference Therapy, Dose, and Mode of Administration:	**Group 3**: Placebo-to-match (2 x 1 ml SC injections) administered weekly

Criteria for Evaluation:

Safety:	Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests, physical examinations, and vital sign assessments at various time points during the study.
Efficacy:	The primary efficacy endpoint is the change from Baseline in DAS28(CRP) at Week 12. Secondary endpoints include the proportion of subjects who achieve DAS28(CRP) $\leq$ 3.2 and the proportion of subjects who achieve DAS28(CRP) < 2.6 at Week 12.
Pharmacokinetics:	Plasma concentrations of GS-5745 will be determined.
Exploratory:	PPD

Statistical Methods:

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug. The primary endpoint is mean change from Baseline in DAS28(CRP) at Week 12. The primary analysis will compare each of the two GS-5745 treated groups to the placebo group using a mixed model repeated measures (MMRM) approach.

Secondary endpoints include the proportion of subjects who achieve DAS28(CRP) $\leq$ 3.2 at Week 12 and the proportion of subjects who achieve DAS28(CRP) < 2.6 at Week 12. Cochran-Mantel-Haemszel approach adjusting for the randomization stratification factors will be used to compare each of the GS-5745 treated groups to the placebo group.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group.

A total sample size of 75 subjects is planned for this study. Each of the two GS-5745 treated groups will be compared to the placebo group. A sample size of 25 per group will provide a power of 80% with a

2-sided α level of 0.05 to detect a Minimal Clinically Important Improvement (MCII) in DAS28(CRP) from Baseline of 1.2 at Week 12 between a GS-5745 treated group and the placebo group, assuming a common standard deviation of 1.35 and a 15% early dropout rate.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
β-HCG	beta-human chorionic gonadotropin
ACR	American College of Rheumatology
ACR 20/50/70	American College of Rheumatology 20/50/70% improvement
AE	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCP	cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CIA	collagen-induced arthritis
CFR	Code of Federal Regulations
CK	creatine kinase
cm	Centimeter
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common Toxicity Criteria for Adverse Events
DAS28	Disease Activity Score
DMARD	disease modifying anti-rheumatic drug
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eSAE	electronic serious adverse event
ESDD	Early Study Drug Discontinuation
ESR	erythrocyte sedimentation rate
EU	European Union
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
g	Gram
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
HAQ-DI	Health Assessment Questionnaire Disability Index
HBsAg	hepatitis B surface antigen

HCV Ab	hepatitis C antibody
Hep B core Ab	Hepatits B Core Antibody
HIV	human immunodeficiency virus
CRP	C-Reactive Protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICH E3	ICH Guideline for Structure and Content of Clinical Study Reports
ie	that is
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IR	inadequate response
IRB	Institutional Review Board
IU	international units
IUD	intrauterine device
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MMP9	matrix metalloproteinase 9
MTX	Methotrexate
NSAID	nonsteroidal anti-inflammatory drug
PCR	Polymerase Chain Reaction
PE	physical examination
PK	Pharmacokinetics
Q1	first quartile
Q3	third quartile
QA	quality assurance
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formula
RA	rheumatoid arthritis
RF	rheumatoid factor
RNA	Ribonucleic acid
s	Second
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan

SC	Subcutaneous
SD	standard deviation
SDAI	Simplified Disease Activity Index
SF-36	Short Form (36) Health Survey
SJC	swollen joint count
SmPC	Summary of Product Characteristics
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
TNF- IR	tumor necrosis factor – Inadequate Response
ULN	upper limit of normal
US, USA	United States, United States of America
VAS	visual analogue scale
VS	Vital signs

1. INTRODUCTION

1.1. Background

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US) {Helmick et al 2008}. Rheumatoid arthritis manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the ages of 40 and 50 years, and women are affected 3 times more often than men {Lawrence et al 1998}. While the cause of RA is still not completely understood, aberrant B-cell activation, T-cell costimulation, osteoclast differentiation, and cytokine release all have been implicated in its pathogenesis. Subjects with RA experience a high risk of disability and mortality {Arthritis Foundation 2008}.

Despite recent advances in RA treatment, including TNF-targeted therapeutics, a number of subjects experience insufficient response to these agents and continue to suffer from disease-related symptoms, as well as incurring joint damage. Matrix metalloproteinase 9 (MMP9) has been reported to play an important role in the progression of RA, and is known to be expressed in human RA as well as animal models of disease. The role of MMP9 in disease progression in RA is supported by findings in the MMP9 knockout mouse, which is significantly protected against increased disease severity in a collagen-induced arthritis model of RA, whereas matrix metalloproteinase 2 (MMP2) knockout mice develop more severe disease than littermate controls {Itoh et al 2002}. Tartrate resistant acid phosphatase (TRAP) positive mononuclear and multinucleated cells are often found in the synovium at the sites of cartilage and bone destruction. TRAP-positive multinucleated cells from RA subjects, including osteoclasts, secrete MMP9 and are key participants in joint destruction {Tsuboi et al 2003}. Furthermore, MMP9 has been shown to play a critical role in osteoclast invasion {Engsig et al 2000}. Studies in a variety of different disease models and correlations in human disease support a role for MMP9 in driving inflammation through increased vascular permeability and through promoting the activation or increasing the bioavailability of cytokines and growth factors {Gearing et al 1995}. Selective inhibition of MMP9 by GS-5745 has the potential to slow and/or halt progression of bone and joint erosion, as well as to reduce inflammation in RA subjects.

1.2. GS-5745

1.2.1. General Information

For further information on GS-5745, refer to the current investigator's brochure for GS-5745.

1.2.2. Preclinical Pharmacology and Toxicology

GS-5745 is a fully humanized high-affinity monoclonal IgG_4 antibody that is a selective and potent allosteric inhibitor of MMP9. In subjects with Ulcerative Colitis (UC) and Crohn's disease, MMP9 expression is strongly induced and is associated with progressive disease. Matrix metalloproteinase 9 (MMP9) expression has also been shown in the synovial tissue in human RA, and in macrophages and other cells in lung tissue in human COPD. Murine surrogates of GS-5745, with similar epitope specificity and inhibitory activity, have demonstrated significant anti-inflammatory and tissue-protective activity in rodent models of colitis and arthritis. Similarly, MMP9 is expressed in a number of solid tumors such as lung, gastric, and pancreatic adenocarcinomas and lung squamous cell and hepatocellular carcinomas. In addition, anti-MMP9 antibodies demonstrated efficacy in a mouse xenograft model of human colorectal carcinoma with respect to both primary tumor volume and weight. Unlike pan-MMP inhibitors, specific inhibition of MMP9 with a murine surrogate of GS-5745 showed no evidence of inducing musculoskeletal symptoms or pathology in a rat model. Furthermore, there were no effects on safety pharmacology endpoints (clinical observations, EGCs, respiratory rate) in the 4-week repeat-dose toxicity studies at doses of up to 100 mg/kg/dose.

The toxicology program consists of completed 4-week and 26-week repeat-dose intravenous (IV) toxicity studies in both rats and monkeys and a human tissue cross-reactivity study. To support the transition to a subcutaneous (SC) formulation, a SC local tolerability study in rats was conducted and the 26-week toxicity studies in rats and cynomolgus monkeys included both IV and SC routes.

Findings associated with GS-5745 treatment in the 4-week repeat-dose toxicity studies have been limited to reversible physeal hypertrophy in rats, an expected response to MMP9 inhibition, and reversible increased adrenal gland weight in female monkeys at all doses, which was associated with slight hypertrophy of the zona fasciculata in a single 100-mg/kg/dose female monkey. In the 26-week studies, there were no findings of toxicological concern in rats or cynomolgus monkeys following weekly IV or SC administration at doses up to 100 mg/kg and 150 mg/kg, respectively. The lack of physeal hypertrophy observed in the rat 26-week study is presumably due to the reversible nature of this finding as longitudinal bone growth and growth plate closure slows/completes. There were no adverse injection site reactions observed in the 26-week studies, and no adverse findings in the local tolerability study. There was no specific GS-5745 staining observed in normal human tissues.

The rat and rabbit embryo fetal development studies and the rat fertility study have also been completed. As expected, there was no specific GS-5745 staining observed in normal human tissues. At doses of GS-5745 up to 100 mg/kg/dose IV, data indicate no test article-related maternal or fetal effects in rats and rabbits, and no test article-related effects on male or female fertility in rats.

In summary, in these studies at exposure multiples of the anticipated clinical exposure, there was no evidence of GS-5745 induced hematological changes, no effects on immune system organ weights, including thymus, spleen and lymph nodes, and no observed immunosuppressive effect.

1.2.3. Clinical Trials of GS-5745

Gilead is currently conducting clinical trials with GS-5745 in ulcerative colitis, Crohn's Disease, solid tumors, chronic obstructive pulmonary disease, and cystic fibrosis (CF). For information on all Gilead sponsored trials for GS-5745, please refer to the current Investigators Brochure for GS-5745.

1.3. Rationale for This Study

1.3.1. Clinical Rationale

Current RA treatment guidelines from the American College of Rheumatology and European League Against Rheumatism (ACR/EULAR), the 2013 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis and the EULAR Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs: 2013 Update, respectively, recommend switching subjects who have an inadequate response to TNF inhibitors (TNF-IR) to an alternate TNF inhibitor or another class of biologic. Several biologics have been approved for use in TNF-IR subjects, but responses to these single biologics tend to be lower than in TNF inhibitor naïve RA subjects. Thus, there remains an unmet need particularly for the TNF-IR subjects.

Gilead Sciences, Inc. (Gilead) conducted a Phase 1 double-blind, randomized, placebo-controlled study in RA subjects in Europe. Subjects were randomized in a 4:1 ratio to receive an IV infusion of GS-5745 (400 mg) or matched placebo every 2 weeks for a total of 3 infusions (Days 1, 15, and 29). Subjects participated in the study for up to 117 days; which included up to 2 screening visits, 3 infusion visits, 4 follow-up visits, and 2 follow-up telephone calls. The screening visits were conducted a maximum of 15 days before the first infusion. Follow-up visits occurred on Days 3, 8, 36, and 43, and follow-up telephone calls occurred on Days 57 and 100. Subjects were required to have a mean C-reactive protein (CRP) value during Screening $\geq$ 8 mg/L and not allowed to have received recent concomitant RA biologics within a defined period prior to Screening or during the study.

No subjects were considered mild or in remission. In contrast to GS-5745-treated subjects at Day 43, the placebo group had no subjects with mild disease activity or remission. All 3 placebo subjects at Day 43 had moderate disease activity.

Interestingly, these clinical improvements occurred despite a lack of major change in CRP values. Among subjects treated with GS-5745 during the study (n=15), the mean values at Baseline and Day 43 were 37.21 (18.688) mg/L and 21.10 (18.977) mg/L, respectively, a mean decrease of 6.11 (22.577) mg/L. Among subjects treated with placebo (n=3), the mean CRP values at Baseline and Day 43 were 16.57 (11.153) mg/L and 12.46 (10.572) mg/L, respectively, a mean decrease of 4.12 (5.922) mg/L.

No deaths, serious adverse events (SAEs), AEs that caused study drug discontinuation, or pregnancies were reported in this study. All AEs were Grade 1 or Grade 2 in severity. The most frequently reported AEs among subjects randomized to GS-5745 (ie, reported for ≥ 10% of subjects in the GS-5745 group) were hypertension (2 of 15 subjects, 13.3%) and nasopharyngitis (2 of 15 subjects, 13.3%). Overall, no AE/SAE safety signals were noted during the study. All graded laboratory abnormalities were Grade 1 or Grade 2 in severity. One subject (6.7%) randomized to GS-5745 had a Grade 2 chemistry abnormality, and 2 subjects (13.3%) randomized to GS-5745 had Grade 2 hematology abnormalities. No clinically important changes from Baseline in vital signs or ECG results occurred during the study. Overall, these data indicate GS-5745 was well tolerated during the study and that GS-5745 may be beneficial in subjects with RA.

Though the sample size of the Phase 1 RA study is small and the study duration brief, results indicate GS-5745 may have clinical activity in RA. It is not yet known if the magnitude of the clinical response is sufficiently high that GS-5745 could be differentiated as a single agent for RA. However, combining GS-5745 with a TNF-α inhibitor has the potential to augment the clinic benefit of either agent alone. Therapeutic strategies that employ combinations of conventional and biologic disease-modifying antirheumatic drugs have demonstrated superior clinical responses compared to single agent approaches. Combining 2 biologics is an extension of this treatment strategy and offers an approach to achieving the treat-to-target approach to RA management specified in the ACR/EULAR treatment guidelines. Given the lack of significant immunosuppression seen with GS-5745, clinical benefit may be obtained in subjects with RA when combining this agent with a biologic DMARD, as GS-5745 is postulated to decrease RA disease activity via novel pathways which are unique or at least partially unique from those inhibited by anti-TNF or methotrexate (MTX).

The efficacy of the combination of a mouse specific anti-MMP9 agent (AB0046) and an anti-TNF agent (Enbrel) was evaluated in a collagen induced arthritis (CIA) mouse model. Using a chronic model of advanced disease, therapies were administered after an average clinical score of > 2 was reached (Day 28) and were continued through Day 43. Treatment with AB0046 and Enbrel, each on its own or in combination, resulted in significant efficacy with respect to clinical scores as compared to the control group for: ankle diameter, paw swelling, body weight change, and histopathological assessment of soft tissue damage, bone erosion, and joint destruction. At Day 43, treatment AB0046 and Enbrel combined therapy resulted in significant improvements in

clinical score ($p < 0.05$ as compared to control group). Moreover, the combination of AB0046 and Enbrel resulted in a trend for superior therapeutic benefit as compared to each agent alone; however a statistically significant difference as compared to each single agent was not observed. Similar findings were apparent for other metrics such as body weight and histopathology. In an alternative analysis that evaluated the number of limbs scored with mild or no disease at the end of treatment, combination therapy yielded a significant benefit over each individual agent or a beneficial trend as compared to Enbrel alone. Analysis of complete blood count at the end of study revealed no abnormalities in any treatment group. Overall, these data indicate that the addition of anti-MMP9 to anti-TNF therapy does not compromise the activity of either agent, is well tolerated in this murine model as judged by both body weight and complete blood count, and could potentially provide a larger therapeutic benefit in arthritis.

Unlike other current biologics marketed to treat RA, the mechanism of action of GS-5745 as a protease inhibitor of MMP9 does not have a direct suppressive effect on systemic immune function. As of 17 Jan 2016 GS-5745 has been administered to approximately 255 subjects in multiple indications (oncology, ulcerative colitis, Crohn's disease, rheumatoid arthritis, and chronic obstructive lung disease) and thus far no safety signals have been identified, including any risk of serious or opportunistic infections, despite many of the subjects enrolled in these studies being immunocompromised due to cancer chemotherapy or receiving systemic immunosuppression to treat their primary disease.

1.3.2. Toxicology Rationale

Based on the toxicology profile of GS-5745 and the known clinical safety of TNF inhibitors, there is no evidence of overlapping toxicity with the TNF inhibitors and combination toxicology testing of GS-5745 is not considered warranted.

1.3.3. Dose Selection

Clinical experience includes IV dosing of GS-5745 up to 1800 mg every other week in oncology indications, which has been well tolerated.

In the Phase 1 RA study (GS-US-373-1276) dosing of GS-5745 400 mg IV every 2 weeks for a total of 3 infusions demonstrated clinical benefit and was well tolerated.

Subsequent to study GS-US-373-1276 in RA, a SC formulation of GS-5745 was developed for use in inflammatory diseases. A bridging study was performed in healthy subjects (Study GS-US-326-1430) and demonstrated that the SC formulation of GS-5745 has an absolute bioavailability of 44.1%. Subsequent studies of GS-5745 in inflammatory disease have used the SC formulation.

The doses selected for this RA study are based upon clinical experience with the SC formulation of GS-5745 in ulcerative colitis. In a Phase 1 study of subjects with moderately to severely active UC (GS-US-326-0101) subjects received IV (every other week) or SC GS-5745 (weekly) for one month. Of the 10 subjects dosed with SC GS-5745 once weekly, 4 subjects (40.0%) met the Mayo Score criteria for response, 2 out of 10 subjects (20.0%) met the criteria for remission, and

5 subjects (50.0%) met the criteria for mucosal healing. The weekly SC dose of 150 mg of GS-5745 was well tolerated. Comparable clinical responses were observed in subjects who received IV GS-5745 at doses 1.0 and 2.5 mg/kg administered every 2 weeks for a total of 3 doses. Accordingly, subsequent studies of GS-5745 are currently being conducted in Crohn's disease (300 mg and 150 mg SC once weekly, and 150 mg SC every other week) and ulcerative colitis (150 mg SC weekly, and 150 mg SC every other week). Additionally, there has been no apparent difference in GS-5745 PK between subjects with UC and RA, indicating similar target inhibition between subjects with UC and RA at the same dose of GS-5745. Based upon these findings, in this RA study, SC doses of 300 mg and 150 mg once weekly were selected based on dose (150 mg) shown to have evidence of efficacy in ulcerative colitis, and a higher dose of 300 mg which represent the top dose level in ongoing trials in Crohn's disease.

1.4. Risk/Benefit Assessment for the Study

GS-5745 is currently being evaluated for the treatment of solid tumors, UC, Crohn's Disease, chronic obstructive pulmonary disease, cystic fibrosis, and RA. From the adverse events (AEs) reported in completed and ongoing trials in these indications, no drug-related safety signal has been identified. Also, no drug interactions or contraindications have been reported.

Infusion reactions, anaphylaxis, or immune mediated inflammatory responses are possible with monoclonal antibodies. Potential risks with GS-5745 may include local injection site reactions and the rare possibility of hypersensitivity or allergic reactions. A single hypersensitivity reaction was observed after a second infusion in a UC subject. The subject was evaluated at the local emergency room and was discharged home in satisfactory condition. Despite this single hypersensitivity reaction after an IV infusion of GS-5745, it should be noted that GS-5745 is not considered to be a 'high risk' agonist as it acts by antagonism and targets MMP9. In this study, GS-5745 will be administered in a SC formulation which reduces the risk of severe hypersensitivity reactions. In addition, the first 2 doses of study drug in the blinded and OLE periods of the study will be administered at the study site clinic so that subjects can be observed for possible unexpected injection reactions.

While TNF inhibitors have demonstrated great benefit for subjects with more difficult to treat RA, this class of biologics has a mechanism of action that down modulates cellular and humoral immunity and has demonstrated an increased risk for infections{Ali et al 2013}. Furthermore, treatment of RA subjects with TNF inhibitors combined with other biologics that directly affect the immune system {Genovese et al 2004, Greenwald et al 2011, Weinblatt et al 2006} all increased the risk of serious infections.

In contrast, GS-5745 is a biologic with a mechanism of action that does not directly affect innate or adaptive immunity. It binds to and inhibits the zinc-dependent endopeptidase, MMP9, an enzyme that degrades extracellular matrix proteins. Pre-clinical and clinical studies performed to date with GS-5745 or rodent equivalent have failed to observe an increased risk of infections. Thus, combining GS-5745 with a TNF inhibitor is not expected to increase the risk of serious infections. As a safety precaution this study protects study enrollees by screening for TB and chronic viral hepatitis, limiting the number and amount of immune modulating agents and excluding subjects with a previous history of serious infections.

Lastly, investigators will closely monitor the subjects for the possible infections. In parallel the DMC will review safety data at scheduled intervals to assess for possible emerging safety signals.

With the above safety measures in place, this clinical study will provide information about the benefits of GS-5745 in combination with TNF-inhibitors in RA subjects and potentially provide an additional therapy to improve the health and quality of life of subjects with this condition. These benefits are believed to outweigh any potential risks.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

To assess the efficacy of GS-5745 versus placebo as an add-on therapy to a TNF inhibitor and methotrexate in subjects with moderately to severely active rheumatoid arthritis (RA)

The secondary objectives of this study are as follows:

- To assess the safety and tolerability of GS-5745 versus placebo as an add-on therapy with a TNF inhibitor and methotrexate in subjects with moderately to severely active RA
- To assess the pharmacokinetics (PK) of GS-5745 as an add-on therapy with a TNF inhibitor and methotrexate in subjects with moderately to severely active RA

The exploratory objectives of this study are as follows:

PPD

3. STUDY DESIGN

3.1. Endpoints

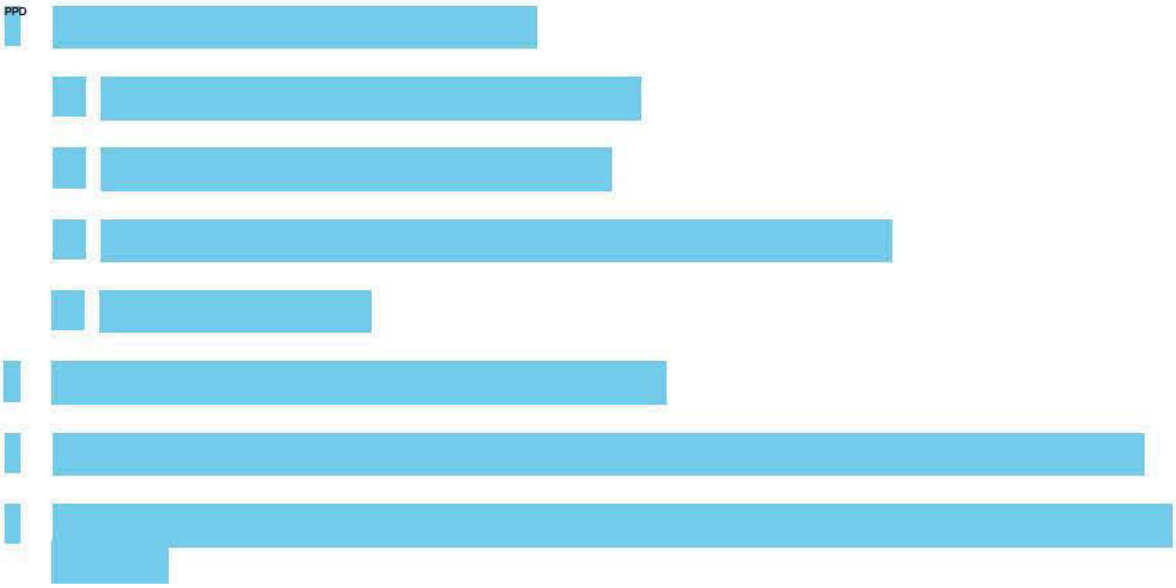
The primary endpoint of this study includes:

- Change in DAS28(CRP) from Baseline to Week 12

The secondary endpoints of this study include:

- Proportion of subjects that achieve DAS28(CRP) $\leq$ 3.2 at Week 12
- Proportion of subjects that achieve DAS28(CRP) < 2.6 at Week 12
- Assess plasma concentrations of GS-5745

The Exploratory Endpoints include:



3.2. Study Design

This is a Phase 2, double-blind, placebo-controlled, randomized, multi-center study evaluating the efficacy and safety of GS-5745 as add-on therapy in subjects with moderately to severely active RA.

Subjects will be stratified by their DAS28(CRP), either DAS28(CRP) > 5.1 or DAS28(CRP) > 3.2 and $\leq$ 5.1, and by their prior number of RA biologics used (< 3 or >= 3).

Subjects will receive SC injections of study drug (GS-5745 or placebo) once a week for 12 weeks in the blinded period eligible subjects who complete the blinded period of the study may participate in the open label extension (OLE), where they will receive weekly SC injections of 300 mg of GS-5745 for 52 weeks, in addition to continuing their current TNF inhibitor and MTX.

3.3. Study Treatments

Following completion of screening assessments, eligible subjects will be randomized in a blinded fashion in a 1:1:1 ratio as follows:

Group 1:

GS-5745 300 mg (2 x 1 mL GS-5745 [150 mg/ml] SC injections) administered weekly (N=25)

Group 2:

GS-5745 150 mg (1 x 1 mL GS-5745 [150 mg/ml] + Placebo-to-match 1 x 1 mL SC injection administered weekly (N=25)

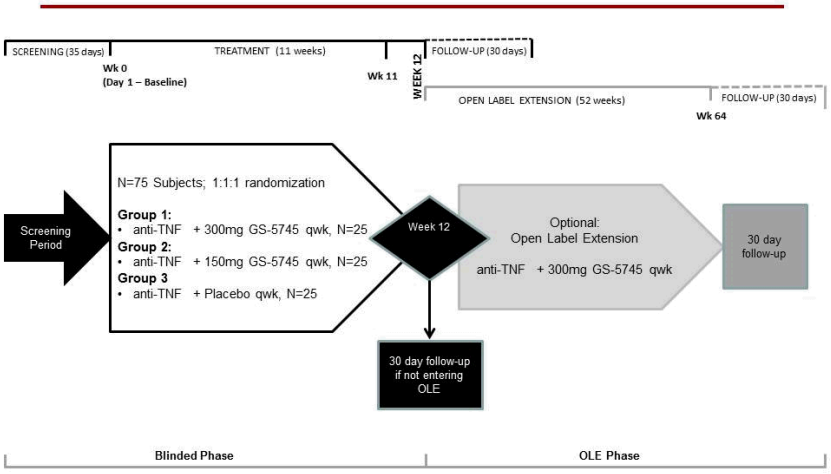
Group 3:

Placebo-to-match (2 x 1 ml SC injections) administered weekly (N=25)

3.3.1. Open Label Extension

At the Week 12 visit, eligible subjects (from Group 1, 2 or 3) who choose to participate in the OLE will start weekly, open-label, SC injections of 300 mg of GS-5745 for 52 weeks, in addition to their current SC administration of a TNF inhibitor and continued MTX.

Figure 3-1. Study Schema



3.3.2. Home Administration of Study Drug

Weekly clinic visits during the study may pose a significant burden to study subjects. This burden must be balanced against the need to monitor subjects during the early doses of study drug.

In the blinded period, SC study drug administration will occur at the study site on Day 1, Weeks 1, 4 and 8. Subjects will remain at the study site for at least 30 minutes after the first 2 injections of study drug for observation. The observation period may be extended as per judgment of the investigator. After receiving SC instruction during the first 2 drug SC injections, subjects (or their caretaker) who are judged capable by the investigator, may administer remaining study drug injections at home, except for doses that coincide with the in-office visits, which should be administered at the study site.

In the OLE, study drug administration will occur at the study site for the first 2 doses (Weeks 12 and 13). Subjects will remain at the study site for at least 30 minutes after the first 2 injections of study drug for observation. Subjects (or their caretaker) may administer remaining study drug injections at home, except for doses that coincide with the in-office visits, which should be administered at the study site.

Study subjects should return used and unused syringes to the investigator's office

3.4. Duration of Treatment

Subjects will receive 12 SC injections of weekly study drug (GS-5745 or placebo) in the blinded period and up to 53 weekly doses of GS-5745 in the OLE.

3.5. Study Subject Interruption and Discontinuation Criteria

3.5.1. Study drug interruption considerations:

The Medical Monitor should be consulted prior to study drug interruption when medically feasible.

Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the Gilead medical monitor*:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Gilead medical monitor.
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immuncompromised individual, and the subject should be closely monitored.

NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

3.5.2. Study drug discontinuation considerations:

The Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement
- Evidence of active HBV during study, as evidenced by HBV DNA positivity

- Evidence of active HCV during the study, as evidenced by HCV RNA positivity
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study (Appendix 5)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee
- Subject use of prohibited concurrent therapy may trigger study drug discontinuation: consultation should be made with the Gilead medical monitor

Subjects who permanently discontinue study medication for any reason are to receive standard of care treatment for their RA as determined by the investigator, and those subjects should be encouraged to continue study visits and procedures, if deemed medically appropriate by the investigator. Subjects who permanently discontinue study medication for pregnancy should not continue in the study; if there are any questions regarding permanent discontinuation, these should be discussed with the Sponsor.

Subjects withdrawing from the study should complete the ESDD and 30-day follow-up visits.

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow-up. These must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

3.6. End of Study

The end of this study is defined as 30 days after the last subject's final study visit in the OLE.

3.7. Biomarker Testing

Samples for biomarker research will be stored for up to 15 years after the end of the study. These analyses are exploratory and individual subject results will not be provided to the study subjects or to the investigators. Because biomarker science is a rapidly evolving area of investigation, it is

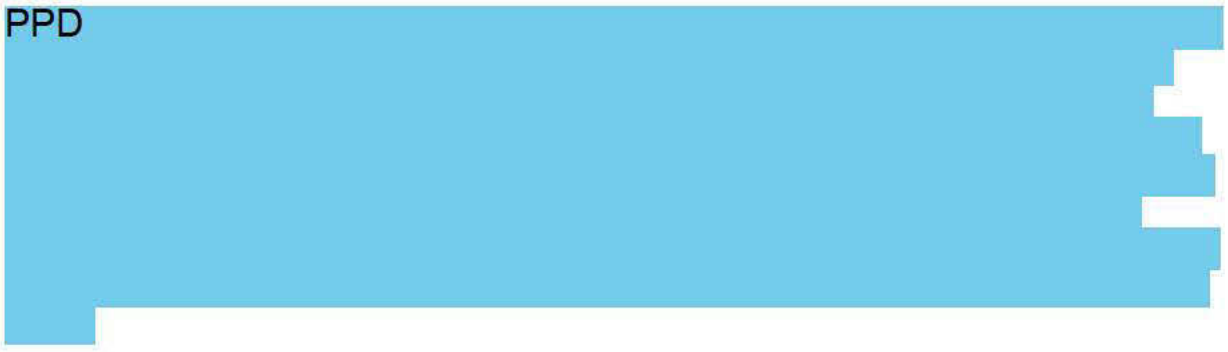
not possible to specify prospectively all tests that will be done on the specimens provided. The collection and analysis of research specimens may facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

3.7.1. Biomarker Samples to Address the Study Objectives:

Blood will be collected in this study and will be used to evaluate the association of biomarkers with the safety and clinical response to GS-5745 and to increase the knowledge and understanding of the biology of RA and/or autoimmune and related inflammatory diseases. The samples collected can be used for the validation of diagnostics. The specific analyses will include, but are not be limited to, MMP9 levels and activity in blood, as well as pathways relevant to TNF signaling. The testing of MMP9 and markers related to MMP9 pathway, inflammation, autoimmunity, and TNF pathways is based upon the current state of scientific knowledge. The plan may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

In addition to the study-specific informed consent to be signed by each subject, a separate, specific signature will be required to document a subject's agreement to allow the use of the remainder of their already collected biomarker and PK specimens for optional future research. The specimens retained for optional future research will be used to increase our knowledge and understanding of the biology of the study disease and related diseases and to study the association of biomarkers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

3.7.2. Biomarker Samples for Optional Genomic Research



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 75 subjects with moderately to severely active RA who are currently treated with a TNF-inhibitor and MTX for at least 12 weeks will be enrolled in the study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of the study procedures; subjects who need a representative/guardian to provide consent are not permitted in this study

2) Male or female subjects between 18 and 80 years of age inclusive, at time of signing initial informed consent

3) Diagnosis of RA according to the 2010 ACR/EULAR classification criteria (See Appendix 8), confirmed at Screening

4) Subjects must meet Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA (Appendix 6), at Screening

5) Must have taken oral or parenteral methotrexate (MTX) dosed from 7.5 to 25 mg/week continuously for at least 12 weeks and tolerated this medication, with at least 6 weeks of stable dose (defined as no change in prescription) prior to the first dose of study drug

   - Subjects on MTX may also be on concurrent chloroquine or hydroxychloroquine at a stable dose (defined as no change in prescription) for at least 4 weeks prior to Baseline: if so, they should plan to continue this medication for the duration of the study

   - Must be receiving folic or folinic acid supplementation at Day 1 and throughout the duration of the study, dosed as per investigator

6) Must have $\geq$ 12 weeks of **ongoing** treatment with an approved, SC formulation of TNF inhibitor (adalimumab, certolizumab, etanercept, or golimumab, or marketed biosimilar TNF inhibitor), with at least 6 weeks of stable dose (defined as no change in prescription) defined as:

   - Must have a DAS28(CRP) > 3.2 at Screening

     AND

   - Must have $\geq$ 3 swollen joints and $\geq$ 3 tender joints among 28 joints assessed (using DAS28) at Screening and at Baseline (need not be the same joints)

7) Subjects who have previously received other biologic DMARDs for the treatment of RA are eligible, providing the following washout periods for these have been met:

   - Rituximab – none for at least 6 months prior to Baseline and subject has a CD19+ B cell count in normal range (per central lab) at Screening
   - Infliximab – none for at least 8 weeks prior to Baseline
   - Tocilizumab – none for at least 8 weeks prior to Baseline

8) Non-steroidal anti-inflammatory drugs (NSAIDs) and/or oral corticosteroids (≤ 10 mg prednisone/day or equivalent) at a stable dose (defined as no change in prescription) for ≥ 4 weeks prior to Baseline are allowed and should be continued at the same stable dose throughout the blinded period of the study; PRN NSAIDs for indications other than RA are also allowed.

9) TB Screening: Subjects must meet either a. or b.:

   a. A negative history of TB infection and a negative QuantiFERON® TB-Gold In-Tube test and chest x-ray results (see below). QuantiFERON® tests with inconclusive results may be repeated one time. If the repeat result is also is inconclusive, the subject will be excluded from the study.

   OR,

   b. Subjects with a history of **latent** TB treated with a full course of prophylaxis as per local guidelines, are allowed per investigator judgment. It is the responsibility of the investigator to verify the adequacy of previous treatment and to provide appropriate documentation. *In these cases, no QuantiFERON® test need be obtained.* In addition, must be approved by the medical monitor prior to enrollment. (Any new diagnosis of latent TB or prior untreated/ partially treated latent TB is NOT allowed [ie, subjects who require prophylactic therapy for TB during the study]. Any prior history of active TB [regardless of treatment] is exclusionary.

10) A negative chest x-ray (views per local guidelines) for active TB or other lung disease at Screening; or a chest x-ray within 90 days of Screening if films or report are available for investigator review

11) A negative pregnancy test is required for female subjects of childbearing potential (as defined per protocol), at Screening and at Day 1, prior to dosing of study drug. Female subjects must agree not to become pregnant for 30 days after the last dose of GS-5745

12) Subjects of child-bearing potential (as defined in protocol) must agree to use protocol specified contraceptive measures throughout the study and for 30 days after their last dose of study drug. Female subjects must agree not to become pregnant for 30 days after the last dose of study drug. Male and female subjects taking methotrexate or other drugs should also follow contraception guidelines in the relevant product local label (see Appendix 5)

13) Lactating females must agree to discontinue breastfeeding prior to dosing of study drug and for the duration of the study.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Current treatment with any disease modifying anti-rheumatic drug (DMARD) other than MTX, chloroquine or hydroxychloroquine, or current treatment with other immune modulating/suppressive non-biologic and biologic medications as described in Section 5.4.4

2) Intra-articular corticosteroid injection within 4 weeks of Baseline

3) Any infection requiring oral antimicrobial therapy within 2 weeks prior to Baseline.

4) Previous treatment with GS-5745; known hypersensitivity to GS-5745 or its formulation excipients.

5) Known hypersensitivity to the TNF inhibitor or its formulation excipients that the subject is receiving at Screening

6) Any live or attenuated vaccines within 4 weeks prior to the first dose of study drug or plan to be vaccinated with these vaccines at any time during the study or within 12 weeks after the last dose of study drug.

7) Current inflammatory joint disease, other than RA, such as gout, reactive arthritis, psoriatic arthritis, seronegative spondylarthritis, or Lyme disease, **OR** other current autoimmune diseases such as: systemic lupus erythematosus (SLE), inflammatory bowel disease, fibromyalgia, polymyalgia rheumatica, scleroderma, inflammatory myopathy, mixed connective tissue disease, or other overlap syndrome that would interfere with the evaluation of RA or require protocol prohibited medication; (subjects with Sjogren's syndrome or controlled thyroiditis as defined by the investigator are not excluded)

8) Active systemic involvement secondary to RA such as vasculitis or Felty's syndrome

9) History of any of the following within 12 months of Baseline:

   a) infection requiring parenteral antibiotics or hospitalization,

   b) any life-threatening infection,

   c) sepsis

10) History of infected prosthetic joint at any time, with the prosthesis still in situ

11) Significant blood loss (>450 mL) or transfusion of blood product within 12 weeks prior to Day 1.

12) Tests performed at the central laboratory at Screening that meet any of the criteria below (out of range lab values may be rechecked one time, after consultation with the sponsor or its designee, before subject is considered a screen-failure):

   a) Hemoglobin <8.0 g/dL (International System of Units [SI]: <80 g/L);

   b) White blood cells <3.0 x 10^3 cells/mm^3 (SI: <3.0 x 10^9 cells/L);

   c) Neutrophils <1.5 x 10^3 cells/mm^3 (SI: <1.5 x 10^9 cells/L);

   d) Lymphocytes <0.5 x 10^3 cells/mm^3 (SI: <0.5 x 10^9 cells/L);

   e) Platelets <100 x 10^3 cells/mm^3 (SI: <100 x 10^9 cells/L);

   f) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.0x ULN;

   g) Total bilirubin level ≥2x ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented;

   h) Estimated glomerular filtration rate <40 mL/min/1.73m^2 based on the Modification of Diet in Renal Disease (MDRD) formula (See Appendix 10).

   i) Positive HIV serology during screening

   j) Evidence of active Hepatitis B Virus (HBV) infection. Subjects with positive HBV surface antigen (HBsAg) at screening are excluded from the study. Subjects with negative HBsAg who have positive HBV core Ab, require reflex testing for HBV DNA. Subjects with positive HBV DNA at screening will be excluded. Subjects with positive HBV core Ab, and negative HBV DNA are eligible for study entry, per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care, and require ongoing monitoring with blood tests for HBV DNA every 3 months, as outlined in the schedule of assessments. Subjects with evidence of active Hepatitis B during the study, as evidenced by DNA positivity, will be discontinued from the study drug as outlined in the protocol (Section 3.5.2).

   k) Evidence of active Hepatitis C Virus (HCV) infection. Subjects with a positive HCV Ab at Screening require reflex testing for HCV RNA. Subjects with a positive Hep C RNA at Screening will be excluded. Subjects with a positive HCV Ab, but a negative HCV RNA are eligible, per investigator judgment, but require ongoing HCV RNA monitoring every 3 months. Subjects with evidence of active Hepatitis C during the study, as evidenced by RNA positivity, will be discontinued from the study drug as outlined in the protocol (Section 3.5.2).

13) Any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study, per judgment of investigator

14) Current malignancy, or a history of malignancy or lymphoproliferative disorder within 10 years of Screening, except:

    a) Carcinoma in situ of the cervix that has been successfully treated

    b) Basal or squamous cell cancer or other localized non-melanoma skin cancer that has been successfully treated

15) Participation in another investigational drug study within 1 month of Screening (for a small molecule) or within 3 months or 5 drug half-lives prior to Screening, whichever is longer (for a biologic agent)

16) Male subjects who are unwilling to refrain from sperm donation during the study and for 90 days after their last dose of study drug

17) Female subjects who are unwilling to refrain from egg donation or egg harvesting (for the purpose of current or future fertilization) during the course of the study for 30 days after their last dose of study drug and

18) Presence of any condition that could, in the opinion of the investigator, compromise the subject's ability to participate in the study, eg, substance abuse, alcoholism, or an unstable psychiatric condition.

19) Known hypersensitivity to rubber or latex

20) Have undergone surgical treatments for RA including synovectomy or arthroplasty within the last 12 weeks prior to Screening or planned such surgery during the study

21) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), or within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, or a new or significant ECG finding at Screening, or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participating in the study.

22) Any chronic, uncontrolled medical condition which would put the subject at increased risk during the study, such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per judgment of the investigator.

4.3.1. Screen Failures

- Subjects who do not meet the Inclusion/Exclusion criteria for entry into the study ("screen failures") may be rescreened one time in selected cases (with written permission from the Sponsor); for example, to meet a drug washout period.
- Subjects who do not enter the study due to administrative reasons (for example, exceeding the screening window due to issues with appointment scheduling or obtaining results of laboratory data) may be rescreened one time (with written permission from the Sponsor); this rescreening option is in addition to the rescreening permitted above.

- Neither of the rescreening options is to be used to recheck a subject who is likely unsuitable for the study, for example, to check whether their chronically abnormal laboratory test is closer to normal range.
- Subjects who are permitted to rescreen must repeat the informed consent process and sign a new form; they will receive a new subject number. In these cases, certain screening tests do not need to be repeated (per investigator judgment) if they were performed within 60 days of rescreening consent, these include: chest x-ray and QuantiFERON® TB-Gold In-Tube test

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects will be assigned a screening number at the time of consent. The Day 1 visit and randomization cannot occur until the investigator has received the results of the screening tests and subject eligibility has been confirmed. Once eligibility is confirmed, each subject will be assigned a unique subject number, which will not be reassigned to any other subject.

At the Day 1 visit, subjects will be randomized in a 1:1:1 ratio to Dosing Group 1, 2, or 3. Randomization will be stratified by disease activity at Screening: DAS28(CRP) > 5.1 or DAS28(CRP) > 3.2 and ≤ 5.1. In addition, subjects will be stratified by prior use of RA biologics including the TNF inhibitor being administered during Screening (>=3 or <3). The IXRS will assign blinded study drug numbers at each study drug administration visit, and study drug will be dispensed to the subject in a blinded fashion until Week 12.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-5745 and Placebo

5.2.1. Formulation

GS-5745 for SC injection is formulated as a sterile, aqueous buffered solution in a single-use pre-filled syringe (PFS) with a plunger stopper. The buffered solution contains acetate at pH 5.0, sucrose and polysorbate 20 added for stabilization. Each PFS is intended to deliver 1 mL containing 150 mg GS-5745 at a concentration of 150 mg/mL.

Placebo for SC injection is formulated as a sterile, aqueous buffered solution in a single-use PFS with plunger stopper. The buffered placebo solution contains the same excipients as the GS-5745 formulation: acetate at pH 5.0, sucrose and polysorbate 20. Each PFS is intended to deliver 1 mL of buffered solution.

5.2.2. Packaging and Labeling

GS-5745 and placebo for SC injection are supplied in 1 mL type I clear single-use glass PFS with a coated elastomeric plunger stoppers.

Study drug(s) to be distributed to centers in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Gilead or designated distribution depots will distribute study drug to centers as per Good Manufacturing Practice (GMP) requirements.

5.2.3. Storage and Handling

GS-5745 and placebo for SC injection are to be shipped and stored under refrigeration between 2 to 8 °C (36 to 46 °F). Storage conditions are specified on the label.

Upon arrival at the clinical center, the study drug products must be stored in a secure area, accessible only to authorized study site personnel. To ensure drug stability and proper product identification, the drug products should be stored in the kits in which they are supplied until needed.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body.

5.3. Dosage and Administration of GS-5745 and Placebo to Match

Subcutaneous injections of study drug (GS-5745/PTM) should be administered to 1 of 4 locations: to the right thigh, left thigh, right abdomen, or left abdomen (abdominal injections should be made at or below the level of the navel, avoiding the area within 5 cm [two inches] of the navel). If a subject is dosing their TNF inhibitor medication on the same day as their study drug, the subject should be instructed to inject their TNF inhibitor in a different site than the study drug. Information regarding which site was used for study drug injection will be collected throughout the study.

GS-5745 or placebo will be administered SC at the research center at Day 1 and Weeks 1, 4 and 8 during the blinded part of the study. All injections should be delivered within 1 hour of the first SC injection. The investigator or a qualified designee must be present during the administration of SC injections at Day 1 and Week 1. After training for SC injection at the study site, the subject will be allowed to administer the remaining weekly SC study drug doses at

home, except for those doses which coincide with scheduled study visits; in those cases, the study drug should be administered at the site, under direction of study staff (to enable timing for PK blood draws or other study procedures).

During the OLE portion of the study, GS-5745 will be administered SC at the research center at Weeks 12 and 13. Afterwards, subject will administer the subsequent weekly SC study drug doses at home, except for those doses which coincide with scheduled study visits; in those cases, the study drug should be administered at the site, under direction of study staff (to enable timing for PK blood draws or other study procedures).

In any part of the study, if the subject has a body temperature of > 38ºC (100.4ºF), or the subject feels unwell or is otherwise unfit to receive study drug at a given scheduled weekly injection, the subject should not be administered study drug. In consultation with the medical monitor, the Investigator may delay dosing until the parameters above have resolved.

If a subject fails to dose the study drug within the 3 day window of the scheduled SC weekly dose during the blinded part of the study, they should contact the study site for instructions on dosing. The investigator and the Medical Monitor will determine if a late dose of study drug is acceptable to administer or if the dose should be skipped. If a subject misses >3 of the first 12 scheduled doses of study drug, the Gilead medical monitor should be contacted to discuss if the subject should be withdrawn from the study. See below for missed doses of concomitant medications (Section 5.4.1).

5.4. Concomitant Medications

At each study visit, the study center will record any and all medications taken by the subject since the last visit or during the visit (as applicable), as well as the indication for each medication. Concomitant medications include prescription medications, non-prescription medications, therapies, vitamins, herbal medicines, and other dietary supplements. Site staff should confirm that concomitant anti-TNF dosing, weekly MTX dosing, and folic acid supplementation (or equivalent) are ongoing.

5.4.1. Missed Doses of Concomitant Medications (TNF and MTX)

- TNF inhibitor:

If a subject fails to dose their SC TNF inhibitor within +3 days (for weekly TNF inhibitors), +5 days (for biweekly TNF inhibitors) or +9 days (for monthly TNF inhibitors), of their scheduled TNF inhibitor dose date during the blinded part of the study, they should contact the study site for instructions on dosing. The investigator will determine if a late dose of TNF inhibitor should be administered, or if the dose should be skipped. If the site determines (per concomitant medication reporting) that a subject has missed >25% of their TNF inhibitor doses, the Gilead medical monitor should be contacted to discuss whether the subject should be withdrawn from study drug.

- Methotrexate:

If a subject fails to dose their weekly MTX within +3 days of their scheduled MTX dose date during the blinded part of the study, they should contact the study site for instructions on dosing. The investigator will determine if a late dose of MTX should be administered, or if the dose should be skipped. If the site determines (per concomitant medication reporting) that a subject has missed >25% of their MTX doses, the Gilead medical monitor should be contacted to discuss whether the subject should be withdrawn from study drug.

5.4.2. Allowed Concomitant Medications:

- Antimalarials (hydroxychloroquine, chloroquine): Are allowed provided that the subject is on a stable prescription for at least 4 weeks prior to the first dose of study drug. This stable dose should be maintained through Week 12; dosing of these medications may be adjusted by the investigator after the Week 12 visit is complete. If these medications are to be discontinued, they should be discontinued at least 4 weeks prior to the first dose of study drug.

- Chronic NSAIDs/COX-2 inhibitors, opioids, tramadol, and acetaminophen/paracetamol: Are allowed provided that the subject is on a stable prescription for at least 4 weeks prior to the first dose of study drug. This stable dose should be maintained through Week 12; dosing of these medications may be adjusted by the investigator after the Week 12 visit is complete. If these medications are to be discontinued, they should be discontinued at least 2 weeks prior to the first dose of study drug.

  NOTE: <u>All</u> analgesics (including chronic NSAIDs) should be held on the day of study visits, until after all study procedures for that day have been completed, as much as possible.

- Low dose oral corticosteroids: Doses ≤ 10 mg of prednisone (or equivalent) per day are allowed, and should remain stable (defined as no change in prescription) through Week 12. During the OLE, oral corticosteroids may be modified as per judgment of the investigator. However, the chronic daily dose should not exceed 10 mg/day of prednisone (or equivalent). If these medications are to be discontinued, they should be discontinued at least 4 weeks prior to the first dose of study drug.

- Other medications (eg, hormone replacement therapy, antihypertensive agents, etc.) for chronic stable medication conditions: Are allowed and should remain stable (defined as no change in prescription) during the study, as much as possible.

5.4.3. Rescue Therapy

During the blinded part of the study, no rescue therapies are allowed, including additional (PRN) doses of analgesics (eg, acetaminophen/paracetamol or opioids) for RA. However, if the study investigator determines that a corticosteroid injection in a joint (that is not included in DAS28) is medically indicated, a dose of up to 20 mg methylprednisolone (or equivalent) is allowed. In these cases, the medical monitor should be notified as soon as possible.

During the OLE (after the Week 12 visit has been completed), a maximum of 40 mg methylprednisolone (or equivalent) will be allowed as intra-articular rescue medication. This total allowed corticosteroid dose may be divided into separate intra-articular injections.

Also in the OLE (after the Week 12 visit has been completed), intra-articular hyaluronate sodium injections may be administered in accordance with the local label, in no more than 2 joints in any 6 month study period.

Any joints injected during the blinded or OLE parts of the study will be classified as non-assessable for the remainder of the study.

5.4.4. Disallowed (Prohibited) Concomitant Medications

The disallowed **DMARDs**, **Biologic Response Modifiers** and **Other Medications** below require a drug-specific washout period prior to dosing of study drug as defined below. These medications are also not allowed at any time during the 12 week blinded period of the study or during the OLE period, unless otherwise specified:

Synthetic DMARDs

- **Minocycline/doxycycline, penicillamine, and sulfasalazine**: Discontinued for 4 weeks prior to the first dose of study drug.
- **Leflunomide** (Arava®): Discontinued 12 weeks prior to the first dose of study drug or 4 weeks prior to first dose of study drug, if an appropriate washout method has been utilized (either cholestyramine or activated charcoal).
- **Auranofin** (Ridaura®), injectable gold (aurothiglucose or aurothiomalate) or equivalent: Discontinued for 4 weeks prior to the first dose of study drug.
- **Tofacitinib** (Jeljanz®), a Janus kinase inhibitor (Jak inhibitor): Discontinued for 4 weeks prior to the first dose of study drug. Any other JAK inhibitor should also have been discontinued for 4 weeks prior to the first dose of study drug.

Biologic Response Modifiers (Biologic DMARDs)

All of the following are to have been discontinued prior to entry into this study and are prohibited while the subject is receiving study drug:

- **All TNF inhibitors except the TNF inhibitor being administered during Screening**: Discontinued for 12 weeks prior to the first dose of study drug.
- **Abatacept** (Orencia®), **anakinra** (Kineret®), **tocilizumab** (Actemra®): Discontinued for 12 weeks prior to the first dose of study drug.
- **Rituximab** (Rituxan®) or other selective B lymphocyte depleting agents (either marketed or investigational): Discontinued for 6 months prior to the first dose of study drug. Must have normal B cell count as per I/E criteria (see Section 4.2).
- **Other bDMARDS** (including investigational drugs): Should be discussed with the Sponsor.

Other Medications

- **Intramuscular or intravenous corticosteroids:** None should be administered within 30 days prior to the first dose of study drug, or during the blinded part of the study. However, in the OLE, these medications may be used as judged medically necessary by the study investigator.

- **Intra-articular injections:** None should be administered during the blinded part of the study, except for special circumstances (see Section 5.4.2).

- **Cyclosporine, tacrolimus or other calcineurin inhibitors, azathioprine, mycophenolate:** Discontinued 4 weeks prior to the first dose of study drug and are prohibited while the subject is receiving study drug (including during the OLE).

- **Alkylating agents (**eg chlorambucil or cyclophosphamide**)**: Any prior treatments with these agents is exclusionary and these drugs are prohibited while the subject is receiving study drug (including during the OLE).

- **Prosorba Device/Column:** Discontinued 4 weeks prior to the first dose of study drug.

- **Investigational NSAIDS** (including COX-2 inhibitors): Discontinued 4 weeks prior to the first dose of study drug.

- **Any investigational drug** not mentioned elsewhere: Prohibited while the subject is receiving study drug (including during the OLE).

5.5. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits

- Record the date, subject number, subject initials, the study drug kit number dispensed

- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Study drug return and disposal will be performed as outlined in Section 9.1.7

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to randomization or enrollment and throughout the study.

Once consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, eligible subjects will be randomized to study treatment as described in Section 5.1.

The study center will not be released to initiate dosing until:

- The Institutional Review Board (IRB) or Ethics Committee (EC) reviewed and approved the study and the informed consent document;
- All required regulatory documents have been submitted to and approved by Gilead or the CRO;
- A master services agreement and/or study agreement is executed;
- The site initiation meeting has been conducted by the Gilead clinical monitor (or designee).

The initiation meeting will include a review of the protocol, the IB, and investigator responsibilities.

6.2. Pretreatment Assessments

6.2.1. Screening Visit (Day -35 to Day 1)

Written informed consent must be obtained from each subject before initiation of any visit procedures. After a subject has provided informed consent, the investigator will determine if the subject is eligible for participation in the study. Subjects will be screened within 35 days before randomization to determine eligibility for participation in the study. The assessment will include a review of the Inclusion/Exclusion criteria and completion of all Screening Visit procedures as outlined in Appendix 2.

Subjects who do not meet the eligibility criteria will be excluded from randomization and may be considered for rescreening one time for the study in consultation with the Sponsor or its designee

Screening Assessments will include confirmation of RA diagnosis; medical /surgical history; vital signs (VS) to include blood pressure, pulse, respirations, temperature, and weight; height; complete physical exam (CPE); 12 lead ECG; and central laboratory tests including Rheumatoid Factor, anti-CCP, hematology, urinalysis, urine drug screen, chemistry panel, serum ß-HCG (women of childbearing potential), QuantiFERON –Gold (QFT), HIV Serology, Hepatitis B and C serologies (if positive reflex testing for positive HBV DNA and HCV RNA), CRP, Estimated Glomerular Filtration Rate (based on MDRD study equation), TSH and HbA1c and flow cytometry for subjects who have been on rituximab. Also included are 66 swollen and 68 tender joint count assessment, Patient's and Physician's Global Health Assessment, and Patient's Assessment of Pain.

A chest x-ray if one has not been performed within 90 days of Screening and films or report available for investigator review

RA disease activity will be determined by DAS28(CRP) at Screening for inclusion criteria and for randomization stratification purposes on Day 1.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days after start of screening for randomization into the study.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Baseline/Randomization Assessments (Day 1)

Subjects who met the eligibility criteria will undergo the evaluations listed in Appendix 2.

Day 1 evaluations will include the following: Review of AEs and concomitant medications, vital signs, targeted physical exam, urine pregnancy test, clinical laboratory examinations (hematology, urinalysis, chemistry panel, hsCRP, and Erythrocyte Sedimentation Rate [ESR]; performed locally using the Westergren method), and anti-drug antibodies (ADA) blood draw, biomarker blood draws, study drug administration, tender and swollen joint counts, patient global assessment of pain, physician assessment of global disease activity, patient global assessment of disease activity, SF-36, Health Assessment Questionnaire (HAD-QI), and optional collection of blood for DNA analysis (genomic testing).

All Day 1 procedures and assessments should be completed prior to randomization and study drug administration.

6.3. Blinded Treatment Assessments (Week 1 through Week 12)

All visit tests and procedures should be completed as indicated in Appendix 2. Joint counts, patient global assessment of pain, physician's assessment of global disease activity, patient's

assessment of physical function, SF-36, HAD-QI should be administered prior to lab draws and study drug administration, as much as possible.

On-Treatment Assessments

- Concomitant medications
- Vital signs
- CPE at Week 12 and at ESDD if not done in the prior 12 weeks
- Targeted Physical exam (TPE) at all other visits
- 12 lead ECG at Week 12 and ESDD if not done in the prior 12 weeks
- hsCRP
- ESR
- urinalysis
- Clinical laboratory tests: hematology, chemistry panel on Study Day 1, Weeks 1, 4, 12, and at the 30-day safety follow-up (if applicable)
- Serum β-HCG (Week 12 and 30-day follow-up and ESDD), and urine pregnancy tests on Day 1 and every 4 weeks in women of childbearing potential.
- Subject questionnaires and disease activity measures will be administered at Day 1, Weeks 1, 4, 8 and 12, ESDD and 30-day follow-up (if applicable)
- Subjects with positive HBV Core Ab and/or HCV Ab during Screening should have the respective DNA or RNA PCR test for viral load every 3 months during the study; a positive test for hepatitis virus should lead to study discontinuation as per Section 3.5.2.
- Estimated glomerular filtration rate (eGFR) based on MDRD at week 12, 30 day follow-up and ESDD (calculated at central lab)

Pharmacokinetics/pharmacodynamics:

PK blood draws: PK blood draws will be done prior to dosing at Weeks 1, 4 and 8, anytime on Week 12 and at ESDD (if applicable)

Optional PK Sub-study: PPD

GS-5745 Anti-Drug Antibodies (ADA): Blood draws for ADAs will be done prior to dosing on Study Day 1, Weeks 4 and 8, anytime at Week 12 and the 30-day follow-up visit of the blinded period.

Biomarker Blood Draws: Blood biomarkers will be collected at Day 1, Weeks 4 and 12 in the blinded period of the study. In the OLE biomarker samples will be collected every 3 months starting at week 24.

Genomic Testing

Optional Genomic Testing: PPD

Description of Selected Assessments

Physical Exam

A CPE is required at Screening, Week 12 of the blinded period, and Week 64 of the OLE. A TPE will be performed at other study visits. A limited physical exam is defined as an examination driven by subject signs/symptoms and/or adverse events. Height is captured at screening only.

Vital Signs

Vital signs to be collected include resting blood pressure, pulse, respiratory rate, and temperature.

SF-36 Health Survey

The SF-36 is a health related quality of life instrument consisting of 36 questions belonging to 8 domains in 2 components and covers a 4-week recall period:

- physical well-being: 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items)
- mental well-being: 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items).

Health Assessment Questionnaire Disability Index

The HAQ-DI is a patient reported questionnaire specific for RA. It consists of 20 questions referring to 8 component sets: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Physician's and Patient's Global Assessment of Disease Activity and Patient's Global Assessment of Pain

The physician's and the patient's global assessment of disease activity will be recorded on a 100-mm horizontal visual analog scale (VAS) that ranges from "none" (0 mm, symptom free and no RA symptoms) to "maximum" (100 mm, maximum RA activity). The patient's global assessment of pain will be recorded on a 100-mm horizontal VAS that ranges from "none" (0 mm) to "unbearable" (100 mm).

Joint Assessment

An assessment of 66 joints for swelling and 68 joints for tenderness will be performed. Joints will be assessed and classified as swollen or not swollen and tender or not tender by pressure and joint manipulation upon physical examination. Joint exams should be performed by a trained and experienced joint assessor. Every effort should be made for the same joint assessor to perform the joint exams on the same subject particularly during the blinded period of the study.

Simplified Disease Activity Index

The Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity [visual analogue scale (VAS) 0-10 cm] and level of C-reactive protein (mg/dl).

Clinical Disease Activity Index

Clinical Disease Activity Index (CDAI) is a composite index (without acute-phase reactant) for assessing disease activity. CDAI is based on the simple summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on VAS (0–10 cm) Scale for estimating disease activity

6.3.1. 30-Day Follow-up Visit

Subjects not willing and not eligible to participate in the OLE will return to the clinic for a follow-up visit 30 days after the Week 12 study visit in the blinded period. Thirty days after the Week 64 study visit, subjects will return to the clinic for a follow-up visit. Procedures should be completed as indicated in Appendix 2.

6.4. Open Label Extension Assessments (Week 12 through Week 64)

All OLE test and procedures should be performed as indicated in Appendix 2. All tests and procedures in Week 12 of the blinded period must be completed prior to beginning study drug dosing or procedures for the OLE.

On-Treatment Assessments

- Concomitant medications
- Vital signs
- CPE Week 64 only
- Targeted Physical exam (TPE)
- 12 lead ECG at Week 64 only

- Hematology, chemistry, CRP, urinalysis, and ESR.

- Serum β-HCG (30-day follow-up and ESDD), and urine pregnancy (every 4 weeks) Estimated Glomerular Filtration Rate based on MDRD at 24, 36, 48 and 60 weeks (calculation by central lab)

- Subjects with positive HBV Core Ab and/or HCV Ab during Screening should have the respective DNA or RNA PCR test for viral load performed every 3 months; a positive test for hepatitis virus should lead to study discontinuation as per Section 3.5.2

- In the OLE disease specific questionnaires and activity scores will be administered every 12 weeks, Week 64 and at the 30-day safety follow-up visit.

- Annual chest x-ray (based on local practice guidelines) and negative QuantiFERON® TB-Gold In-Tube test for TB

Pharmacokinetics/pharmacodynamics:

PK blood draws: PK blood draws will be done prior to dosing at Week 24 and anytime at Week 64.

GS-5745 Anti-Drug Antibodies: Blood draws for ADAs will be done prior to dosing at Week 24, anytime at Week 64, and anytime during the 30-day follow-up visit.

Biomarker Blood Draws: Blood biomarkers will be collected every 3 months starting at Week 24.

Additional on-treatment assessments will include symptom-driven physical examination every 6 weeks, and disease-specific questionnaires and activity scores will be administered every 12 weeks, and at the end of the 30-day follow-up visit in the OLE.

Annually: A repeat TB screening (including QuantiFERON® TB-Gold In-Tube test) will be performed (week 54) for subjects continuing in the OLE. A repeat chest x-ray may also be performed, based on local practice guidelines.

6.5. Assessments for Premature Discontinuation from Study/ Early Study Drug Discontinuation Visit

If a subject discontinues study dosing (for example, as a result of an AE or needed for prohibited medication), every attempt should be made to keep the subject in the study and to perform the required study-related follow-up and procedures (see Section 3.5, Criteria for Discontinuation of Study Treatment) as long as it is medically appropriate for the subject to continue. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study and will be asked to return for the Early Study Drug Discontinuation (ESDD) visit. These subjects will not be eligible for the OLE.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion
- The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Adverse Event Instructions

Anaphylaxis is a rare event that may occur after subcutaneous injections of monoclonal antibodies already approved for clinical use or those in clinical development such as such as GS-5745. In an effort to standardize the collection of adverse events that may comprise an anaphylactic event, in this study the definition developed by the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) symposium will be utilized. Information reported by subjects regarding adverse events associated with the study drug will be collected and reviewed; the event causality will be assessed by the study investigator. If any of the AEs reported by the subject fulfill either Criteria 1 or Criteria 2 of the NIAID/FAAN definition of anaphylaxis (See Appendix 11) the event will be classified as anaphylaxis by the site investigator. The event will be considered medically significant and will be reported as an AE or SAE according to guidance in section 7.3. The medical monitor will be notified immediately. The subject may resume the study dosing in the discretion of investigator in consultation with the medical monitor for review and confirmation. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5 and 7.6

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology that is more likely than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No evidence exists that the adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Appendix 4.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 55-days after last administration of GS-5745 must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 55-days or of the last dose of study GS-5745, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period, however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of GS-5745, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH :	Fax:	1-650-522-5477
	E-mail:	Safety_fc@gilead.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure.

Any SAEs that are attributed to background RA medication (subject's TNF inhibitor or MTX) by the investigator will be forwarded to the relevant marketing authorization holder.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational

medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3.

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:
  http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.

- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.

- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue investigational medicinal product at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to Baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

An occupational exposure with an AE is defined as an exposure to a medicinal product as a result of one's professional or non-professional occupation.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs should also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the pregnant partner should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com.

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of the study is to assess the efficacy of GS-5745 versus placebo as an add-on therapy to a TNF inhibitor and methotrexate in subjects with moderately to severely active rheumatoid arthritis (RA)

The secondary objectives of this study are as follows:

- To assess the safety and tolerability of GS-5745 versus placebo as an add-on therapy with a TNF inhibitor and methotrexate in subjects with moderately to severely active RA
- To assess the pharmacokinetics (PK) of GS-5745 as an add-on therapy with a TNF inhibitor and methotrexate in subjects with moderately to severely active RA

The exploratory objectives of the study are as follows:

PPD

8.1.2. Primary Endpoint

The primary endpoint is change from Baseline in DAS28(CRP) at Week 12.

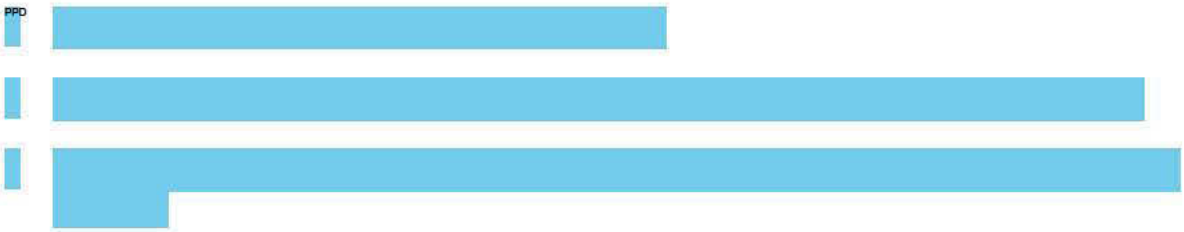
8.1.3. Secondary Endpoints

Secondary endpoints are:

- Proportion of subjects that achieve DAS28(CRP) ≤ 3.2 at Week 12
- Proportion of subjects that achieve DAS28(CRP) < 2.6 at Week 12
- Plasma concentrations of GS-5745

8.1.4. Exploratory Endpoints

PPD



8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set (FAS)

The primary analysis set for efficacy analyses will be the FAS, which includes all randomized subjects who received at least one dose of study drug.

8.2.1.2. Safety Analysis Set

The primary analysis set for safety analyses will be the Safety Analysis Set which includes all subjects who received at least one dose of study drug

8.2.1.3. Pharmacokinetic (PK) Analysis Set

The PK analysis sets includes all subjects in the safety Analysis Set who have the necessary Day 1 and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. BLQ values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation (LLOQ).

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

8.4. Demographic Data and Baseline Characteristics

Demographic and Baseline measurements will be summarized using standard descriptive methods by treatment group and overall.

Baseline characteristics may include prior use of bDMARD, DAS28(CRP), HAQ-DI, SDAI, CDAI, and other variables of interest.

8.5. Efficacy Analysis

The primary endpoint for the study is change from Baseline in DAS28(CRP) at Week 12, which will be analyzed using a mixed model repeated measures (MMRM) approach that includes the fixed effects of treatment, visit, treatment by visit interaction, and Baseline value, and subject as a random effect.

Secondary endpoints include proportion of subjects that achieve DAS28(CRP) $\leq$ 3.2 and proportion of subjects that achieve DAS28(CRP) < 2.6 at Week 12. The response rates between each of the two GS-5745 treated groups and the placebo group will be compared using a stratified Cochran-Mantel-Haenszel (CMH) Chi-square test adjusting for stratification factors in randomization. The difference in response rates between treatment groups and the corresponding 95% confidence intervals will be presented.

Sensitivity analyses may be performed for the efficacy assessment.

Details on efficacy analyses will be described in the statistical analysis plan.

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized by treatment group according to the study drug received.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database. Treatment-Emergent Adverse Events (TEAEs) are:

- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by treatment group. TEAEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and study visit along with corresponding change from Baseline. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly. Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale

8.7. Pharmacokinetic Analysis

The plasma concentration data of GS-5745 will be summarized by nominal sampling time using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) standard deviation, median, minimum, and maximum). PK parameters (C_{max}, T_{max}, C_{last}, T_{last}, AUC_{last}, as applicable) for optional PK sub-study may be listed and summarized using descriptive statistics.

Exposure-response analysis may be explored as appropriate.

8.8. Immunogenicity Analysis

Immunogenicity of GS-5745 will be evaluated based upon the incidence of anti-drug (GS-5745) antibody (ADA) formation. The number and percentage of subjects exhibiting positive ADA results at each specified time point will be summarized. ADA results with supporting data will be included in a listing as well. Impact of ADA on GS-5745 PK, safety, and efficacy may be evaluated as applicable.

8.9. Sample Size

A total sample size of 75 subjects will be required for this study. Each of the 2 GS-5745 treated groups will be compared to the placebo group. A sample size of 25 per group will provide a power of 80% with a two-sided α level of 0.05 to detect a Minimal Clinically Important Improvement (MCII) in DAS28(CRP) change from Baseline of 1.2 at Week 12 between a GS-5745 treated group and the placebo group, assuming a common standard deviation of 1.35 and 15% early dropout rate.

8.10. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim unblinded reviews of safety data at designated scheduled intervals and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with

modifications. The DMC may also provide recommendations as needed regarding study design, The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/EC. The investigator will not begin any study subject activities until approval from the IRB/EC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/EC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/EC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting

written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB, IEC, or local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, and their right to receive clinically relevant pharmacogenomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to

eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB [or] IEC in accordance with local requirements and receive documented IRB [or] IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY CA 94404

STUDY ACKNOWLEDGEMENT

Evaluation of the Efficacy and Safety of GS-5745 as Add-On Therapy to a Tumor Necrosis Factor Inhibitor and Methotrexate Regimen in Subjects with Moderate to Severe Rheumatoid Arthritis

GS-US-373-1499 Protocol Amendment 2 (23 September 2016)

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

DAVID GOSSAGE, MD

PPD

Name (Printed)
David Gossage, MD

23 SEPT 2016

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Visit Schedule

Study Visits: Blinded Period									
Week[a]	**Screening[b]**	**Day 1**	**Week 1**	**Week 4**	**Week 8**	**Week 12[q]**	**ESDD[d]**	**Unscheduled Visit[t]**	**30 Day Follow-up**
Window in Days	**-35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**		**±5**
Written Informed Consent [c]	X								
Confirmation of RA diagnosis	X								
Medical/Surgical History	X								
Complete Physical Exam	X					X	X		
Targeted Physical Exam [e]		X	X	X	X	X		X	X
Concomitant Medications	X	X	X	X	X	X	X	X	
Vital Signs & Weight [f]	X	X	X	X	X	X	X	X	X
Height	X								
Adverse Events	X	X	X	X	X	X	X	X	X
12 lead ECG[s]	X					X	X[s]		
High sensitivity C-Reactive Protein (hsCRP)	X	X	X	X	X	X	X	X	X
Serum ß-HCG Pregnancy Test [g]	X					X	X		X
Urine Pregnancy test [g]		X		X	X			X	
Rheumatoid Factor and anti-CCP antibodies	X								
QuantiFERON-Gold (QFT) blood test	X								
Chest X-Ray [h]	X								
HIV Serology	X								

Study Visits: Blinded Period									
Week[a]	**Screening[b]**	**Day 1**	**Week 1**	**Week 4**	**Week 8**	**Week 12[q]**	**ESDD[d]**	**Unscheduled Visit[t]**	**30 Day Follow-up**
Window in Days	**-35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**		**±5**
Hepatitis BsAg and Core Ab (if positive core Ab, then reflex Hep B DNA)[i] Hepatitis C Ab (if positive, then reflex HCV RNA)[i]	X					X			
Estimated Glomerular Filtration Rate (based on MDRD study equation) performed by central lab	X					X	X		X
Erythrocyte Sedimentation Rate (ESR) Local Lab		X	X	X	X	X	X	X	
Hematology[j]	X	X	X	X		X	X	X	X
Chemistry[k]	X	X	X	X		X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
66 swollen and 68 tender joint count assessment	X	X	X	X	X	X	X	X[t]	X
Thyroid Stimulating Hormone (TSH)	X								
Glycated Hemoglobin (HbA1c)	X								
CD19 Flow cytometry (patients who have taken rituximab or any B cell depleting agent)	X								
Disease Specific Questionnaire and Activity Scales	X	X	X	X	X	X	X	X[t]	X
Health Assessment Questionnaire Disability Index (HAQ-DI)		X	X	X	X	X	X		X

Study Visits: Blinded Period									
Week[a]	**Screening**[b]	**Day 1**	**Week 1**	**Week 4**	**Week 8**	**Week 12**[q]	**ESDD**[d]	**Unscheduled Visit**[t]	**30 Day Follow-up**
Window in Days	**-35 days**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**		**±5**
Short Form (36) Health Survey (SF-36)		X	X	X	X	X	X		X
Pharmacokinetics (PK) [l]			X	X	X	X	X		
Optional PK Sub-Study (Day 4 or Day 6) [m]		X							
GS-5745 ADA collection [n]		X		X	X	X			X
Biomarkers (blood samples)		X		X		X			
Optional genomic testing [o]		X							
Randomization		X							
Study Drug Administration [p]		X	X	X	X	X (for subjects continuing to OLE)			
Study Drug Dispensing [r]		X	X	X	X	X (for subjects continuing to OLE)			

a All visits scheduled relative to Day 1
b Evaluations are to be completed within 35 days prior to Day 1.
c Consent must be signed prior to any study evaluations
d Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug, as much as possible
e Symptom-directed physical exam as needed
f Vital Signs include blood pressure, pulse, respirations, temperature
g Women of child-bearing potential only, as defined per protocol
h Chest x-ray should be performed at Screening, unless done in the previous 90 days, with films or results available at the site
i If HB Core Ab and/or HC Ab are positive during screening but their respective DNA or RNA PCR tests are negative, the PCR test should be repeated every 3 months
j Refer to Appendix 12 for complete laboratory assessments
k Refer to Appendix 12 for complete laboratory assessments
l Prior to dose at Week 1, 4, 8, and anytime at week 12 and ESDD (if applicable)
m Anytime on Day 4 (+/-1) or Day 6 (+/- 1) after Day 1 dose (for subjects who consent to optional PK substudy only)

n Prior to dose on Study Days 1, Week 4, 8, anytime on Week 12 , and 30 day follow-up
o Collection of blood for DNA analysis will be optional for subjects and will be collected at Day 1 or at any other visit during the course of the study
p Subjects will receive weekly SC injections of GS-5745. SC Study Drug Administration will occur at the study site on study Day 1, Week 1, Week 4, and Week 8. Subjects will remain at the study site for 30 minutes after the injection for observation on Day 1 and Week 1 The observation period may be extended as per judgment of the investigator. After receiving SC instruction at the study site during the first 2 drug SC injections, subjects judged capable will be allowed to self-administer weekly SC injections at home.in the blinded and OLE periods. Subjects not eligible or choosing not to participate in the OLE will come in for Week 12 visit assessments will not be administered study drug. Subjects that are eligible and choose to participate in the OLE will receive their first dose of study drug in the OLE of the study on Week 12 after completing all the requirements of Week 12 of the blinded period of the study.
q Subjects not participating in the OLE will complete all week 12 assessments but will not receive an injection of study drug at the Week 12 visit. If subjects are eligible to participate in the OLE, then subjects complete all Week 12 assessments for the blinded period and then receive the first dose of the drug for OLE.
r Study drug for 4 weekly doses will be dispensed at Weeks 1, 4 and 8
s If not done in the prior 12 weeks. ECGs are to be performed supine
t Per discretion of investigator

Study Visits: Open Label Extension														
Week	**12**	**13**	**19**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64**	**30 Day Follow Up**	**Unscheduled Visit [k]**	**ESDD**
Window in Days	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±3**
Complete physical exam											X			
Targeted physical exam [b]		X	X	X	X	X	x	X	X	X		X	X	X
Vital signs and weight [a]		X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG											X		X [k]	
66 swollen and 68 tender joint count assessment				X		X		X		X	X	X	X [k]	X
Disease Specific Questionnaires and Activity Scales				X		X		X		X	X	X	X [k]	X
HAQ-DI				X		X		X		X	X	X	X [k]	X
SF-36				X		X		X		X	X	X	X [k]	X
Hematology [c]		X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry panel [c]		X	X	X	X	X	X	X	X	X	X	X	X [k]	X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X		X
Erythrocyte Sedimentation Rate (ESR) Local lab			X	X	X	X	X	X	X	X	X	X		X
serum ß-HCG Pregnancy Test [d]												X		X

Study Visits: Open Label Extension														
Week	**12**	**13**	**19**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64**	**30 Day Follow Up**	**Unscheduled Visit [k]**	**ESDD**
Window in Days	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±3**
Urine Pregnancy test at study visits as marked – and every 4 weeks using kit at home (at weeks 16, 20, 28, 32, 40, 44, 52, and 56)[d]				X		X		X		X	X		X	
PK collection [e]				X							X			X
GS-5745 ADA collection [f]				X							X	X		
Biomarker collection	X			X		X		X		X				
C-Reactive Protein (hsCRP)		X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON-GOLD (QFT)									X					X
Chest x-ray (based on local TB screening guidelines)									X					
Estimated Glomerular Filtration Rate (based on MDRD study equation) performed at central lab				X		X		X		X				X

Study Visits: Open Label Extension														
Week	**12**	**13**	**19**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64**	**30 Day Follow Up**	**Unscheduled Visit [k]**	**ESDD**
Window in Days	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±3**
Study Drug Dispensing [g]	X		X	X	X	X	X	X	X	X	no			
Study Drug Administration [h]														
Concomitant medications [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HBV DNA testing for subjects with positive Hep B serology every 3 months if positive HCV RNA testing for subjects with positive hep C serology every 3 mos if positive[j]				X		X		X		X				

a Vital Signs include blood pressure, pulse, respirations, temperature
b Symptom-directed physical exam as needed
c Refer to Appendix 12 for complete laboratory assessments
d Women of child bearing potential only. Patients will be supplied with home urine pregnancy kits and instructed to test every 4 weeks. Site will follow-up with a phone call to obtain and record results (subject with positive test should immediately discontinue study drug and present to the site for a serum pregnancy test). Pregnancy form should be completed should a pregnancy occur,
e Prior to drug dose on (Week 24) and anytime on (Week 64)
f Prior to study dose on (Week 24) and any time on (week 64), the 30 day follow-up
g a 6 week supply of drug (6 doses)will be dispensed at these visits except for Week 12, 13 and week 64 when 1 dose will be dispensed. Site personnel will administer study drug at office visits when drug is dispensed

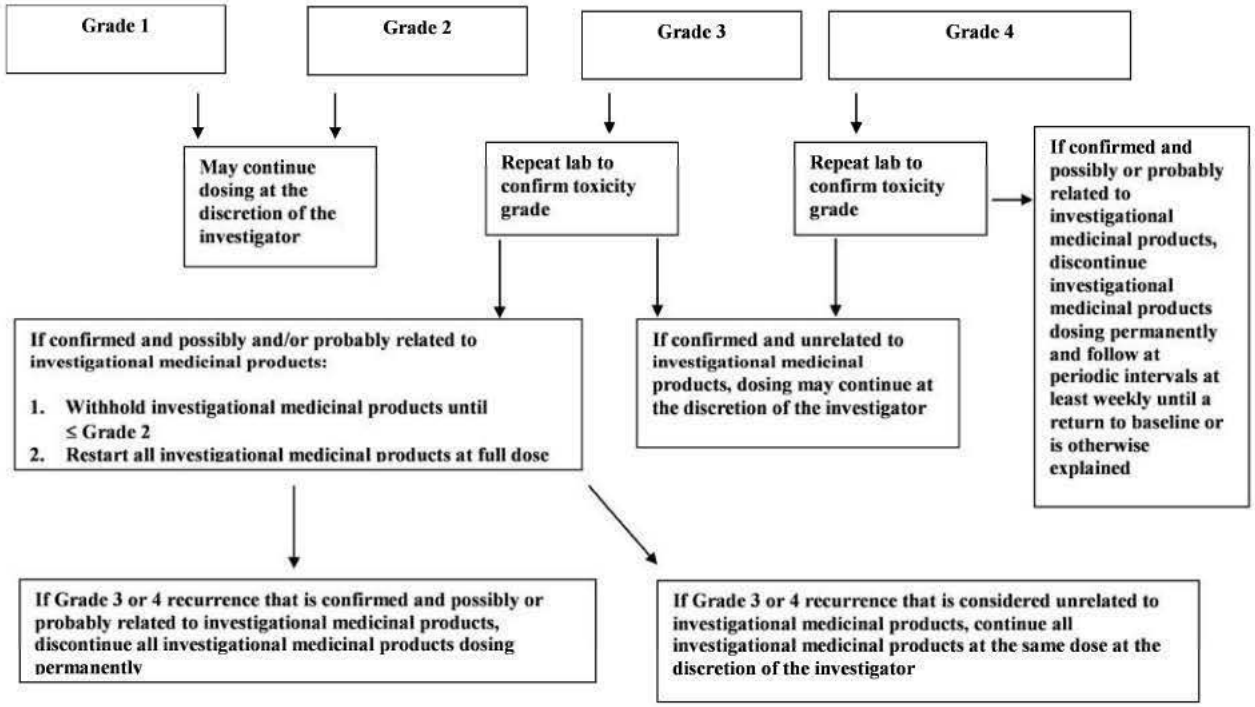
h Patients receive SC injections once a week SC Study drug administration will occur at the study site for the first 2 doses in the OLE at Week 12 and Week 13. Subjects will remain at the study site for 30 minutes after the injection for observation at week 12 and week 13. The observation period may be extended as per judgment of the investigator. If subjects are judged capable, subjects may administer study drug at home for the remainder of the study. SC Study drug administration and anti-TNF administration must be separated in time by at least 24 hours in the blinded and OLE of the study. Subjects should record study drug administration in study drug diary

i Con meds and adverse events will be recorded throughout the study. Patients will be questioned on con med and adverse events at in office visits

j If HB Core Ab and/or HCV Ab are positive during screening, then their respective DNA or RNA PCR test should repeated every 3 months

k Per discretion of investigator

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v4.03 can be accessed from the below link:
http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self -care ADL**.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

The risks of treatment with GS-5745 during pregnancy have not been evaluated in humans. The potential for genotoxicity is not expected given that GS-5745 is a monoclonal antibody. In both the rat and rabbit definitive embryo-fetal developmental toxicity studies, there were no GS-5745-related effects on embryo-fetal survival and growth and no fetal anomalies. In a fertility study in male and female rats, no test article-related effects on reproductive performance and intrauterine survival were observed at any dosage level. In addition, male and female reproductive organ weights were unaffected by GS 5745 at all dose levels. There were no test article-related effects on spermatogenic endpoints at any dose level. The animal peri/post-natal study is ongoing. Women of childbearing potential should be informed of the potential risk and use highly effective methods of birth control during treatment with GS-5745 from screening until 30 days after the end of relevant systemic exposure. A clinically relevant interaction between GS-5745 and contraceptive steroids is not expected because of their distinct metabolic pathways and therefore, hormonal contraception may be used as part of the birth control methods.

Please refer to the latest version of the investigator's brochure of GS-5745 for additional information.

Please refer to the regional prescribing information for details on the potential risks of treatment with methotrexate.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. Subjects taking TNF inhibitor, methotrexate, or other drugs should also follow contraception guidelines in the relevant product local label. Female subjects must agree to one of the following contraceptive methods from Screening throughout the study period until 30 days following the last dose of GS-5745.

- Complete abstinence from intercourse. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception,

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
  - intrauterine device (IUD) with a failure rate of < 1% per year
  - tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - vasectomy in male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

These above described methods are considered *preferred methods* of highly effective contraception in this protocol.

Female subjects who wish to use a hormonally based method must use it in conjunction with a barrier method used either by the female subject or by her male partner. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least 3 months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably a male condom)
  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel

- Transdermal contraceptive patch
- Contraceptive vaginal ring

- Barrier methods (each method must be used with a hormonal method)
  - Male or female condom with or without spermicide
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the last dose of GS-5745. Subjects taking TNF inhibitor, methotrexate or other drugs should also follow guidelines in the relevant product local label

3) Contraception Requirements for Male Subjects

All sexually active male study participants must agree to consistently and correctly use a condom from Baseline until 90 days after the last dose of GS-5745. Female partners of male study subjects should consider using one of the above methods of contraception as well.

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of GS-5745 and follow local guidelines in the product label after the last dose of methotrexate.

Male subjects taking TNF inhibitor, methotrexate or other drugs should also follow guidelines in the relevant product local label.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for partners male subjects) of last GS-5745 dose and 6 months of last dose of methotrexate dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1

Appendix 6. American College of Rheumatology: 1991 Revised Criteria for the Classification of Global Functional Status of Rheumatoid Arthritis*

Criterion	Definition
Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

* Usual self-care activities include dressing, feeding, bathing, grooming and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age and sex specific

Appendix 7. The 2010 American College of Rheumatology –European League Against Rheumatism Collaborative Initiative Classification Criteria for Rheumatoid Arthritis {Aletaha et al 2010}

Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)[c]	
A. Joint involvement[d]	
1 large joint[e]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[f]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)[g]	5
B. Serology (at least 1 test result is needed for classification)[h]	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)[i]	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms[j]	
<6 weeks	0
≥6 weeks	1

a The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

b Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

c Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

d Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

e "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

f "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

g In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular).

h Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

i Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

j Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Appendix 8. American College of Rheumatology Response (ACR 20/50/70): {Felson et al 1995}

ACR Criteria used to assess treatment response levels, reported as % improvement from Baseline. The definition of ACR 20/50/70 is 20/50/70% improvement in tender and swollen joints plus a ≥ 20/50/70 % improvement in at least three of the following five parameters:

- Subject assessment of pain
- Subject Assessment of global disease activity
- Physician assessment of global disease activity
- Subject's assessment of physical function
- Acute-phase reactant (CRP)

The following lists the disease activity measure followed by the method of assessment

1. Tender joint count

ACR tender joint count is an assessment of 68. The joint count should be done by scoring several different aspects of tenderness, as assessed by pressure and joint manipulation on physical examination. The information on various types of tenderness should then be collapsed into a single tender-versus-non tender dichotomy.

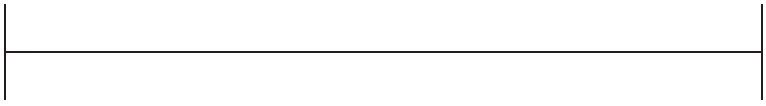
2. Swollen joint count

ACR swollen joint count is an assessment of 66. Joints are classified as either swollen or not swollen.

3. Patient's assessment of pain

A horizontal visual analog scale will be used to assess the patient's current level of pain using a Visual Analog Scale from 0-100 mm.

How much pain have you had because of your condition over the past week? Place a mark on the line below to indicate how severe your pain has been:

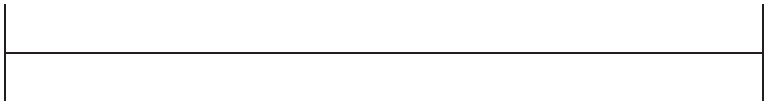


No Pain **Unbearable Pain**

4. Patient's global assessment of disease activity

A horizontal, visual analog scale will be used to provide the patient's overall assessment of how the arthritis is doing.

Place a mark on the line below to indicate how you assess your current arthritis disease activity:



No arthritis activity **Extremely active arthritis**

5. Physician's global assessment of disease activity

A horizontal visual analog scale will be used to measure the physician's assessment of the patient's current disease activity.

Place a mark on the line below to indicate disease activity (independent of the subject's self-assessment):

No Disease Activity **Maximum Disease Activity**

6. Patient's assessment of physical function

The HAQ-DI will be used to provide a patient's self-assessment of physical function.

7. Acute-phase reactant value

C-reactive protein level

Appendix 9. Disease Activity Score DAS28(CRP) {Prevoo et al 1995}

Assessments of RA in patients by the Disease Activity Score (modified to include the 28 joint counts according to Smolen* 1995) will be conducted at the measured timepoints**.** The DAS28-CRP consists of a composite score of the following variables: tender joint count, swollen joint count, CRP, and patient global score. The following equation will be used to calculate the DAS28(CRP). The DAS28(CRP) calculation will be performed by the sponsor.

- DAS28CRP = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96
  - TJC28 = number of joints tender out of 28
  - SJC28 = number of joints swollen out of 28
  - CRP = C-reactive protein
  - GH = 100 mm global health VAS recorded by the patient (patient's global assessment of disease activity)

Place a mark on the line below to indicate how you assess your current arthritis disease activity:

No arthritis activity **Extremely active arthritis**

Appendix 10. Frederica's Formula and Estimated Glomerular Filtration

12-Lead ECG

Subjects will be required to rest in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities. On treatment ECGs should be compared to the subject's Baseline as part of routine safety monitoring. The Frederica Formula will be calculated by the sponsor.

Fredericia Formula (QTcF)

QTc = QT/(RR^0.33)

http://www.thecalculator.co/health/QTc-Calculator-385.html

Estimated Glomerular Filtration

Modification of Diet in Renal Disease (MDRD) formula.- Standardized Formula

175 x serum Creatinine (mg/dl) -1.154 x Age -0.203 x 1.212 (if Black) x 0.742 (if Female)

The eGFR will be calculated by the sponsor.

Appendix 11. Clinical criteria for diagnosing anaphylaxis modified from the NIAID/FAAN Criteria

Anaphylaxis is highly likely when either of the following 2 criteria are fulfilled:

CRITERION 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

OR,

CRITERION 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

Reference: {Sampson et al 2006}

Appendix 12 Laboratory Assessments Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Leukocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV) RBC indices Reticulocyte count ESR (done at local lab) Neutrophil Bands	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Glucose Phosphorus Magnesium Potassium Sodium	Clarity Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal Specific gravity Nitrites. Estimated glomerular filtration rate (based on MDRD study equation Urine microscopic	Urine drug screen at screening visit for: Amphetamines Cocaine Methadone Opiates alcohol Biomarkers Pharmacokinetics B and T cell panels flow cytomertry for CD19 (if required per exclusion criteria) Immunoglobulins: IgA, IgE, IgG, IgM Gs-5745 ADA collection optional genomic testing C-reactive protein (hsCRP) Rheumatoid factor and cyclic citrullinated peptide (RF/CCP) QuantiFERON® TB-Gold TSH HbA1c
		Serology	**Pregnancy**
		Hepatitis BsAg and core Ab (if positive core Ab, then reflex Hep B DNA) repeat every 3 months if positive Ab and neg HBV DNA Hepatitis C Ab (if positive, then reflex HCV RNA) repeat every 3 mos if positive Ab and neg HCV RNA HIV	*In females of childbearing potential:* Serum β-hCG Urine

Ab = antibody
β-hCG = beta-human chorionic gonadotropin
BsAg = B surface antigen